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December 26, 2014

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Drug Master File Staff
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: DMF #: 027320
Holder: McKesson Specialty Health (McKesson)
DMF Subject: Transmucosal Immediate Release Fentanyl (TIRF) Access Program
Re: REMS Shared Program
DMF Type: V
DMF Submission Information: Clinical/Clinical Information
REMS Submission Identifier: Assessment
eCTD Sequence Number: 0014

Dear Drug Master File Staff:

This Type V DMF contains the Risk Evaluation and Mitigation Strategy (REMS) for Transmucosal Immediate Release Fentanyl for the Shared System REMS program.

Included in this submission, please find the REMS Assessment 4 at 3 years.

McKesson states that information provided in this Master File is current and assures that the material furnished will meet the specifications described herein. McKesson also confirms that the Holder obligations are observed.

We request that all information in this file be treated as confidential commercial information to the Food and Drug Administration pursuant to 21 C.F.R. §20.61, and that no information from this file be provided to any unauthorized persons without written consent.

If you have any questions or concerns, please do not hesitate to contact Jann Kochel, U.S. Agent for McKesson, at 610-407-1738 or alternatively via email at jann.a.kochel@accenture.com.

Sincerely,

Jann A. Kochel, U.S. Agent
Accenture, LLP

Attachments: Table of Contents for the submission
Electronic Submission Specifications

Assessment – 3 Years

Module Section	Description
1.2 Cover Letter	Cover Letter w/ Attachments Administrative Information Page
1.16 – Risk Management Plans	REMS History REMS Assessment – 3 Years

Electronic Submission Specifications

This submission is compliant with FDA's Guideline for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).

All files were checked and verified to be free of viruses prior to transmission through the electronic submission gateway. This eCTD has been generated by Accenture, LLP (formerly Octagon Research Solutions Inc.), who has filed an acceptable eCTD pilot with the Center (Pilot Number 900777).

Anti-Virus Program	Symantec Endpoint Protection Edition
Program Version	11.0.5002.333
Virus Definition Date	12/22/2014 rev. 1
Submission Size	Approx. 6 MB

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Statement of Commitment: Attached, please find a signed statement of commitment. The statement certifies that the DMF is current and that McKesson will comply with the statements made in it.

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Modification No.	Date Approved	Documents Affected	Overview of Modification
1	June 5, 2012	• REMS • Prescriber Program Overview • Education Program • Prescriber Enrollment Form • Patient Provider Agreement Form • Patient and Caregiver Overview • Dear Healthcare Provider Letter • Outpatient Pharmacy Overview • Chain Pharmacy Overview • Inpatient Pharmacy Overview • Outpatient Pharmacy Enrollment Form • Chain Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment form • Outpatient Pharmacy Letter • Inpatient Pharmacy Letter • Dear Distributor Letter • Distributor Enrollment Form • Supporting Document	**Sequence 0002**: Edits to Patient-Prescriber Agreement Form, the addition of the Closed System Pharmacy Enrollment Form*, the addition of the newly approved TIRF product, Subsys (fentanyl sublingual spray) and minor editorial changes. *The Closed System Pharmacy Enrollment Form was not formally submitted through the Gateway but was submitted via email on May 18, 2012 and included in the June 5, 2012 FDA approval letter.
N/A	N/A	Assessment Report 1 at 6 months – due 06/28/2012	**Sequence 0003**: Assessment report covering 12/28/2011 to 04/27/2012

Modification No.	Date Approved	Documents Affected	Overview of Modification
2	November 7, 2013	Draft Documents submitted on or before 09/28/2012 • Chain Pharmacy Enrollment Form • Outpatient Pharmacy Enrollment Form • Closed System Pharmacy Overview • Education Program • Frequently Asked Questions (FAQ) • Outpatient Pharmacy Letter • REMS • Supporting Document	**Sequence 0004**: Modification proposed to: • Incorporate closed system pharmacies into the TIRF REMS Access Program • Correct minor inconsistencies between the FDA provided versions and the current PDF versions of REMS materials
N/A	N/A	Assessment Report 2 at 1 year – due 12/28/2012	**Sequence 0005**: Assessment report covering 04/28/2012 to 10/28/2012
2	November 7, 2013	Amendment to 09/28/2012 supplement: • Chain Outpatient Pharmacy Enrollment Form • Independent Outpatient Pharmacy Enrollment Form • Closed System Outpatient Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment Form • Distributor Enrollment Form • Prescriber Enrollment Form	**Sequence 0006**: Modification proposed to: • Revised terminology, processes, and definitions for outpatient pharmacies • Revised attestations for physicians and patients to address concerns regarding patient access • Revised Program Overview and Frequently Asked Questions to improve clarity and content • Updated REMS materials to reflect the completion of the transition phase for the

Modification No.	Date Approved	Documents Affected	Overview of Modification
		• Patient Provider Agreement Form • Chain Outpatient Pharmacy Overview • Independent Outpatient Pharmacy Overview • Closed System Outpatient Pharmacy Overview • Inpatient Pharmacy Overview • Patient and Caregiver Overview • Prescriber Overview • Education Program • Knowledge Assessment • Frequently Asked Questions (FAQ) • Dear Outpatient Pharmacy Letter • Dear Inpatient Pharmacy Letter • Dear Healthcare Provide Letter • Dear Distributor Letter • REMS • Supporting Document • Website Landing Page	TIRF REMS Access Program
N/A	N/A	Assessment Report 3 at 2 years – due 12/28/2013	**Sequence 0007: Assessment report covering 10/29/2012 to 10/28/2013**

Modification No.	Date Approved	Documents Affected	Overview of Modification
N/A	N/A	Safety Surveillance Report #1 – due 03/31/2014	**Sequence 0008: Safety surveillance data covering Q4 2012 to Q3 2013**
3	Approval Pending	• REMS • Prescriber Program Overview • Education Program • Prescriber Enrollment Form • Patient and Caregiver Overview • Independent Outpatient Pharmacy Overview • Chain Outpatient Pharmacy Overview • Closed System Outpatient Pharmacy Overview • Inpatient Pharmacy Overview • Independent Outpatient Pharmacy Enrollment Form • Chain Outpatient Pharmacy Enrollment Form • Closed System Outpatient Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment form • Distributor Enrollment Form • FAQ	**Sequence 0009**: Modification proposed to: • Updated REMS materials to eliminate product specific information which does not impact the safe use of TIRF products • Updated REMS materials to reference the currently approved TIRF products list on the FDA Approved REMS website • Updated REMS materials to remove reference to deactivating patients shown to have multiple prescribers in an overlapping timeframe • Incorporated revised assessment metrics into the Supporting Document • Revised Education Program to emphasize and strengthen appropriate conversion and patient counseling information • Updated REMS and Supporting Document to clarify deactivation of a patient PPAF as opposed to the patient record • Updated pharmacy overview documents and

Modification No.	Date Approved	Documents Affected	Overview of Modification
		• Supporting Document • Website Prototype	• FAQ to call out cash claim requirement • Updated TIRF REMS Access website to incorporate items above and link respective Full Prescribing Information and Medication Guides to DailyMed
N/A	N/A	Cash Claim Information Request Response – due 05/30/2014	**Sequence 0010: Response to 5/16/2014 FDA Cash Claim Information Request**
N/A	N/A	DMF Annual Report – due 08/20/2014	**Sequence 0011: DMF Annual Report**
3	Approval Pending	• REMS • Prescriber Program Overview • Education Program • Knowledge Assessment • Prescriber Enrollment Form • Patient and Caregiver Overview • Independent Outpatient Pharmacy Overview • Chain Outpatient Pharmacy Overview • Closed System Outpatient Pharmacy Overview • Inpatient Pharmacy Overview • Independent Outpatient Pharmacy	**Sequence 0012**: Modification proposed to: • Updated REMS materials to eliminate product specific information which does not impact the safe use of TIRF products • Updated REMS materials to reference the TIRF Products webpage on the TIRF REMS Access website • Updated REMS materials to remove reference to deactivating patients shown to have multiple prescribers in an overlapping timeframe • Incorporated revised assessment metrics into the Supporting Document • Revised Education Program to emphasize and strengthen

Modification No.	Date Approved	Documents Affected	Overview of Modification
		Enrollment Form • Chain Outpatient Pharmacy Enrollment Form • Closed System Outpatient Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment form • Distributor Enrollment Form • FAQ • Supporting Document • Website Prototype	appropriate conversion and patient counseling information • Updated REMS and Supporting Document to clarify deactivation of a patient PPAF as opposed to the patient record • Updated pharmacy overview documents and FAQ to call out cash claim requirement • Updated TIRF REMS Access website to incorporate items above and link respective Full Prescribing Information and Medication Guides to DailyMed • Updated Education Program and Knowledge Assessment to incorporate approved labeling supplement
3	Approval Pending	Unchanged from Sequence 0012, plus: • Dear Healthcare Provider Letter • Dear Outpatient Pharmacy Letter • Dear Inpatient Pharmacy Letter • Dear Distributor Letter	**Sequence 0013**: Unchanged from Sequence 0012, plus: • Dear Healthcare Provider Letter • Dear Outpatient Pharmacy Letter • Dear Inpatient Pharmacy Letter • Dear Distributor Letter

Modification No.	Date Approved	Documents Affected	Overview of Modification
N/A	N/A	Assessment Report 4 at 3 years – due 12/28/2014	**Sequence 0014: Assessment report covering 10/29/2013 to 10/28/2014**

Title:	Transmucosal Immediate-Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program 36-month Assessment Report
Reporting Timeframe:	29 OCT 2013 to 28 OCT 2014
Document Number:	Final V1.0
Product Name:	Transmucosal Immediate-Release Fentanyl
Sponsor:	TIRF REMS Industry Group (TRIG) of Companies: Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc. Galena Biopharma, Inc. Insys Therapeutics Inc. Mallinckrodt Pharmaceuticals Meda Pharmaceuticals, Inc. Mylan, Inc. Par Pharmaceutical, Inc.

Confidentiality Statement

TABLE OF CONTENTS

Pg

LIST OF TABLES 5

LIST OF ABBREVIATIONS 7

EXECUTIVE SUMMARY 9

1 BACKGROUND 15

2 REMS GOALS 16

3 SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS 16

3.1 Additional Elements 17

3.1.1 Medication Guide 17

3.1.2 Letters to Healthcare Professionals 17

3.2 Elements To Assure Safe Use 17

3.2.1 Prescription Verification 18

3.3 Implementation System 19

3.3.1 Wholesaler/Distribution Enrollment and Fulfillment 20

3.3.2 The TIRF REMS Access Program Compliance [Metric 22] 20

3.3.3 TIRF REMS Access Program Call Center 20

4 REMS ASSESSMENT PLAN METHODS 20

4.1 Data Sources for REMS Assessments 21

4.1.1 The TIRF REMS Access Program and Product Utilization Statistics 21

4.1.2 Dispensing Activity for Enrolled Pharmacies 22

4.1.3 Program Infrastructure and Performance 22

4.1.4 TIRF REMS Access Program Non-Compliance Plan 23

4.1.4.1 Non-Compliance Monitoring 24

4.1.4.2 Corrective Action Measures 25

4.1.5 Safety Surveillance 27

4.1.6 Periodic Surveys of Patients, Prescribers, and Pharmacies 28

5 RESULTS 29

5.1 REMS Program Utilization 29

5.1.1 Patient Enrollment [Metric 1 and 2] 29

5.1.2 Prescriber Enrollment and Inactivations [Metric 3, 4, 5] 29

5.1.3 Pharmacy Enrollment, Inactivation, and Education [Metric 6, 7, 8] 33
5.1.4 Wholesaler/Distributor Enrollment [Metric 9 and 10] 39
5.1.5 Dispensing Activity [Metric 11, 12, 13,] 40
5.1.6 Barriers or Delays in Patient Access [Metric 14 and 15] 49
5.2 Program Infrastructure and Performance [Metrics 16, 17, 18, 19] 54
5.2.1 Backup System for Prescription Validation [Metric 16] 54
5.2.2 System Interruptions/Errors and Corrective Actions [Metric 17, 19] 54
5.2.3 REMS Call Center [Metric 18] 57
6 TIRF REMS ACCESS PROGRAM NON-COMPLIANCE 58
6.1 Audits 58
6.1.1 Closed System Pharmacy Audits [Metric 20] 58
6.2 Inpatient Hospital Pharmacy Audits [Metric 21] 64
6.3 Stakeholder Non-Compliance [Metric 23, 24, 25, 26, 27, 28] 64
7 SAFETY SURVEILLANCE 93
7.1 Adverse Event Reporting [Metric 29] 93
7.2 TRIG Sponsor Adverse Event Data of Interest [Metric 30] 93
7.3 Number of Adverse Events of Special Interest 93
7.4 TIRF Product Surveillance Data [Metric 31] 121
7.4.1 Background 121
7.4.2 Poison Center Program 122
7.4.3 Treatment Center (TC) Program 122
7.4.4 College Survey Program 123
7.4.5 Impaired Healthcare Workers Program 123
7.4.6 Results 123
7.4.7 Population Rates 123
7.4.8 Prescription Rates 124
7.4.9 Pediatric Exposures 125
7.4.10 Comparison of Cases from Reporting Period 1 to Reporting Period 2 126
8 PERIODIC SURVEYS OF STAKEHOLDERS 127
8.1 Key Risk Messages 127
8.2 Patient KAB Survey 128

8.2.1 Background and Survey Statistics 128
8.2.2 Patient Survey Results 128
8.3 Pharmacy KAB Survey 129
8.3.1 Background and Survey Statistics 129
8.3.2 Pharmacy Survey Results 129
8.4 Prescriber KAB Survey 130
8.4.1 Background and Survey Statistics 130
8.4.2 Prescriber Survey Results 130
8.5 Overall Conclusion for KAB Results: 131
9 FDA COMMUNICATIONS 131
10 POST-APPROVAL STUDIES AND CLINICAL TRIALS 132
11 OVERALL CONCLUSIONS 132
12 APPENDICES 135
12.1 Safety Surveillance Aggregate Line Listing Preferred Terms 136
12.2 RADARS® System Program Report 136
12.3 RADARS® System Program Report Protocol 136
12.4 Periodic Stakeholder Surveys 136
12.4.1 Patient KAB Survey 137
12.4.2 Pharmacy KAB Survey 138
12.4.3 Prescriber KAB Survey 139

LIST OF TABLES

Table 1 TIRF Medicines 15
Table 2 Assessment Report Periods 16
Table 3 Non-Compliance Activity Monitoring 24
Table 4 Corrective Action Guideline 26
Table 5 Patient Enrollment 29
Table 6 Prescriber Enrollment 30
Table 7 Prescriber Inactivations 30
Table 8 Prescribers Pending Enrollment 32
Table 9 Pharmacy Enrollment 33
Table 10 Pharmacy Inactivations 35
Table 11 Pharmacies Pending Enrollment 38
Table 12 Distributor Enrollment 39
Table 13 Distributor Inactivations 39
Table 14 Prescriptions from Outpatient Pharmacies That Did Not Encounter Any REMS-Related Rejections Prior to Being Authorized for Dispensing 41
Table 15 Prescriptions from Outpatient Pharmacies That Encountered at Least One REMS-Related Rejection Prior to Being Authorized for Dispensing 43
Table 16 Time to Authorization for a Prescription that Experienced at Least One Initial REMS-Related Rejection 47
Table 17 Number of Prescription Authorizations per Closed System Pharmacy 48
Table 18 Prescriptions Dispensed During the First 10 Days after Passive Patient Enrollment 51
Table 19 Prescriptions Dispensed Beyond the First 10 Days after Passive Patient Enrollment Without a PPAF 53
Table 20 Current Assessment Period Contact Reasons 57
Table 21 Non-Compliance Activity Reports by Stakeholder in the Current Reporting Period: 29 October 2013 to 28 October 2014 65
Table 22 Non-Compliance Reports in the Current Reporting Period: 29 October 2013 to 28 October 2014 67
Table 23 Number of Cases of Adverse Events of Special Interest 94
Table 24 Rate of Adverse Events by Total Prescriptions and Total Patients 94
Table 25 Cases of Addiction Received from TRIG Sponsors during the Reporting Period: 29 October 2013 - 28 August 2014 95

Table 26 Cases of Overdose Received from TRIG Sponsors during the Reporting Period: 29 October 2013 - 28 August 2014 97
Table 27 Cases of Death Received from TRIG Sponsors during the Reporting Period: 29 October 2013 - 28 August 2014 100
Table 28 Cases of Pediatric Exposures Received from TRIG Sponsors during the Reporting Period: 29 October 2013 - 28 August 2014 120
Table 29 RADARS® System: Data Sources and Specific Events 121
Table 30 RADARS® System Poison Center Program: Reported Exposures by Age Group and Period 126
Table 31 Comparison of TIRF Exposure Data from First RADARS Report to the Incremental Data In the Current Reporting Period: Reports of Abuse by Source of Data 126
Table 32 Comparison of Poison Center Program Data from First RADARS Report to the Incremental Data in the Current Reporting Period 127

LIST OF ABBREVIATIONS

AAPCC	American Association of Poison Control Center
ANDA	Abbreviated New Drug Application
BTP	Breakthrough Pain
CS	College Survey
CAP	Corrective Action Plan
CSR	Call Center Service Representative
DoD	Department of Defense
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HCP	Healthcare Provider
ID	Identification
IR	Immediate Release
KAB	Knowledge, Attitude, and Behavior
MedDRA	Medical Dictionary for Drug Regulatory Activities
NC	Non-Compliant
NCPDP	National Council for Prescription Drug Program
NCRT	Non-Compliance Review Team
NDA	New Drug Application
NDC	National Drug Code
NPI	National Provider Identifier
OTP	Opioid Treatment Program
PMS	Pharmacy Management System
PPAF	Patient-Prescriber Agreement Form
PT	Preferred Terms
RADARS®	Researched Abuse, Diversion and Addiction-Related Surveillance
RCA	Root Cause Analysis
REMS	Risk Evaluation and Mitigation Strategy
REMS edits	Checks conducted by the TIRF REMS Access program to confirm that all safety requirements were met

SKIP	Survey of Key Informants' Patients
SOP	Standard Operating Procedure
TC	Treatment Center
TIRF	Transmucosal Immediate-Release Fentanyl
TIRF Medicines	Transmucosal Immediate-Release Fentanyl product(s)
TIRF REMS Access	REMS program for TIRF medicines
TIRF Sponsors	The group of sponsors that are submitting this REMS
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States
VA	Veteran's Association

EXECUTIVE SUMMARY

The Transmucosal Immediate-Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program was approved by the Food and Drug Administration (FDA) on 28 December 2011 for ABSTRAL®, ACTIQ®, FENTORA®, LAZANDA®, ONSOLIS®, SUBSYS® and generic versions of these TIRF medicines. The TIRF REMS Access Program was successfully launched on 12 March 2012, approximately 11 weeks after REMS approval. The shared system REMS includes a Medication Guide; Elements to Assure Safe Use (ETASU) of prescriber and pharmacy certification, and dispensing to outpatients with evidence of safe use conditions; an Implementation System, and a Timetable for Submission of Assessments.

The initial 6-month REMS Assessment Report was submitted on 28 June 2012, the 12-month assessment was submitted on 29 December 2012 and the 24-month assessment was submitted on 29 December 2013. This fourth REMS Assessment Report (36 months) covers the timeframe 29 October 2013 to 28 October 2014. As per agreement with FDA, safety surveillance analyses necessitated slightly different time periods as noted in the relevant sections within the report.

As of 12 March 2014 the TIRF REMS Access Program has been fully implemented for 2 years. A major focus during this reporting period was re-enrollment of all stakeholders in the program. As part of re-enrollment, stakeholders were re-educated in order to ensure understanding about the safe use and risks of TIRF medicines. For prescribers and pharmacists this included completing a review of the educational materials and successfully completing the Knowledge Assessment and Enrollment Form. Patient-Prescriber Agreement Forms (PPAFs) also expire every 2 years. This requires prescribers to re-counsel their patients about safe use and risks. Both attest to their understanding of the safe use and risks by signing a new PPAF. Extensive efforts are made using multiple modalities to reach all stakeholders whose enrollment status or PPAF is nearing expiration. Re-enrollment activities continue ensuring appropriate access to TIRF medicines.

Prescriber Enrollment

At the end of this reporting period, a total of 12,749 prescribers are enrolled in the TIRF REMS Access Program. A total 2,027 were newly enrolled prescribers. During the reporting period, a total of 4,731 prescribers were inactivated, with 4,658 (98.5%) due to expiration of their enrollment at some time during the reporting period. A total of 3,089 prescribers successfully re-enrolled during the reporting period. A few prescribers were inactivated because they opted out of the program or were deceased.

During this reporting period, a total of 71 prescribers attempted enrollment but were still pending 3 to 6 months after initiating the enrollment process and a total of 265 prescribers were pending enrollment for longer than 6 months since initiating the enrollment process. The most common reasons for pending enrollment were: no attestation, training not complete, and knowledge assessment failure on the first attempt.

Pharmacy Enrollment

At the end of this reporting period, a total of 37,775 pharmacies are enrolled in the TIRF REMS Access Program. A total of 1,585 pharmacies were newly enrolled in the TIRF REMS Access Program. Of the 1,585 newly enrolled pharmacies, 788 were chain pharmacy stores, 588 were independent outpatient pharmacies, 182 were inpatient pharmacies, and 23 were closed system pharmacy locations. During the reporting period, a total of 5,040 pharmacies were inactivated, with 4,802 due to expiration of their enrollment at some time during the period.

A total of 50 pharmacies attempted enrollment but were still pending 3 to 6 months after initiating the enrollment process and a total of 229 pharmacies were pending enrollment for longer than 6 months since initiating the enrollment process. The most common reasons for pending enrollment were pending test transaction verification, no attestation and training not complete.

Distributors Enrollment

During the reporting period 1 newly enrolled distributor and 21 distributors that re-enrolled in this reporting period. There were 10 distributors inactivated during the reporting period due to expiration of enrollment; 2 of these distributors had re-enrolled by the end of the reporting period.

Patients

During the current reporting period, 9,744 patients had an enrolled status in the TIRF REMS Access Program. Because patients are passively enrolled with their first prescription, they are not required to re-enroll at any point. Instead, prescribers must renew a patient's PPAF every 2 years. By the design of the program, a patient enrollment status will never change to inactivated.

Dispensing Activity

A total of 159,560 prescriptions were presented for dispensing in the current reporting period including 158,612 prescriptions from non-closed system pharmacies and 948 prescriptions from closed system pharmacies. Of the total prescriptions presented for dispensing, 90.9% were approved for dispensing without encountering any REMS-related rejections.

Of the total 159,560 prescriptions presented for dispensing, 3,738 prescriptions encountered at least one REMS-related rejection due to failure to meet REMS requirements for the prescriber and/or patient and/or pharmacy prior to being authorized for dispensing. The remaining 10,738 prescriptions presented for dispensing encountered at least one REMS-related rejection and were never authorized for dispensing. A single prescription may have been submitted and rejected multiple times.

The average time for an initially rejected prescription to become authorized was 4.9 days.

The number of prescriptions dispensed outside the established PPAF requirements was nearly eliminated as a result of the corrective actions implemented in the previous reporting period. As reported in the 24-month assessment report the TIRF REMS Access Program finalized the required system enhancements on 15 July 2013 to modify the patient matching in order to prevent patients from receiving more than 3 prescriptions without a PPAF and patients from receiving more than 3 prescriptions within the first 10 days without a PPAF.

Non-Compliance and Audits

During the current reporting period, 145 instances of stakeholder non-compliance with the TIRF REMS Access program were reviewed and investigated. This included 120 prescriber reports, 1 wholesaler/distributor report, 17 non-closed system pharmacy reports and 7 closed system pharmacy reports. Five of these closed system pharmacy non-compliance reports were identified during the audits of the 7 enrolled closed system pharmacy entities. Each affected entity was issued a notice through the Non-Compliance Review Team (NCRT) and as a result all investigations have been closed. Details of these cases and actions taken are included in Section 6.1.1 and description of these audits is included in Section 6.1.1.

Audits of 7 closed system pharmacy entities were conducted during this reporting period. Five closed system entities were found to be non-compliant with the TIRF REMS Access Program requirements. These pharmacies were re-educated and issued a notice through the NCRT. All cases have been closed.

As per the TRIG's agreement with FDA, inpatient pharmacy hospital audits have not yet been conducted. The TRIG is developing a process to accomplish inpatient pharmacy audits. Therefore, inpatient pharmacy audit data will be included in the 48-month assessment report.

Safety Surveillance Data

In previous assessment reports, safety surveillance data for TIRF products were presented as an FDA AERS analysis and an analysis of American Association of Poison Control Center (AAPCC) data. Based on FDA feedback, safety surveillance data for this 36-month assessment report and future assessment reports consist of data from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System and aggregate adverse event data from all TRIG sponsors. Spontaneous adverse event data including events of addiction, overdose, death and pediatric exposures, were provided by each sponsor and aggregated into one comprehensive line listing. Comparisons of trends within and between these data sources since the introduction of the TIRF REMS Access Program were not possible for this report, given the change in reporting sources for the events of interest. Future REMS Assessment Reports will evaluate trends across reporting periods.

RADARS® System Data

The initial RADARS® System Report, submitted to FDA in March 2014, included data from 3rd quarter 2012 through 3rd quarter 2013. The RADARS® System Report included within this 36-month assessment report includes data from 3rd quarter 2012 through 2nd quarter 2014, an additional 3 quarters of data.

(b) (4)

Aggregate Spontaneous Adverse Event Data

A total of 367 unique case reports were identified as meeting the criteria for inclusion in the analysis based on case preferred terms and review of the case narrative information. Of the 367 cases, the highest proportion of reports had an outcome of death, and many reports had no cause of death provided. There were 4 reports of addiction, and 2 pediatric exposures. There were no reported overdoses to an identified TIRF product. (Of note, 23 overdose cases from law enforcement are included indicating exposures to purportedly non-pharmaceutical fentanyl.) From the root cause analysis, no reports of inappropriate conversions between TIRF products were identified. Additionally, none of the narratives indicated accidental, unintentional exposures, or non-opioid tolerance. Additional details are included in Section 7.2.

Knowledge, Attitudes, and Behavior (KAB) Surveys

TRIG determined that a desired threshold of 65% or greater would be considered to represent adequate understanding of each concept or key risk message. The same criterion was applied to the 36-month KAB surveys. The purpose of establishing this threshold was to assist TRIG in tracking and monitoring the level of understanding of key risk messages across each wave to determine if the goals of the REMS are being met and if any modification to the REMS is required.

Patient Survey Results

In this 36-month survey, all but one of the questions included as part of the key risk messages had a correct response rate of >69%. There was only one question within a key risk message that had a component with an understanding rate below the threshold of 65% which identified the need to stop taking a TIRF medicine if the around-the-clock opioid pain medicine is discontinued. This concept also scored low for prescribers (61.0%) for this reporting period. One question about the safe use of TIRF medicines, not included as a key risk message, had a component regarding use of a TIRF medicine to treat long-lasting painful conditions not caused by cancer had an understanding rate of 25.3%. This concept also scored low for pharmacists (43.7%). These components were the only components scoring consistently low across all three waves of the patient/caregiver KAB survey. The consistently high level of patient understanding of key risk messages in the 24-month and 36-month surveys indicates that the patient education materials is meeting the goals of the TIRF REMS.

Pharmacist Survey Results

In the pharmacist survey all but one of the questions/components included as part of the key risk messages had a correct response rate of >70%. There was only one question within a key risk message regarding TIRF medicines labeled indications that had a component with an understanding rate below the threshold of 65%, concerning chronic non-cancer pain. This component also had a low correct response rate in the previous survey waves. It should be noted that pharmacist knowledge of uses for which TIRF medicines are not indicated is not a goal of the TIRF REMS. This concept also scored low for patients/caregivers in this reporting period. In addition, there were two questions/components addressing the safe use of TIRF medicines that had a component with an understanding rate below 65%: a cancer patient should not be started on a TIRF medicine and an around-the-clock opioid at the same time (63.3%), and that patients are considered opioid-tolerant if taking an equianalgesic dose of another oral opioid one week or longer. These concepts also scored low for prescribers during this reporting period.

The consistently high level of pharmacist understanding of key risk messages in the 24-month and 36-month surveys indicates that the Education Program for Prescribers and Pharmacists is meeting the goals of the TIRF REMS. Changes will be implemented into the 48-month Pharmacist KAB survey based on FDA feedback received on the 24-month assessment report.

Prescriber Survey Results

In the prescriber survey, of the 21 components of the 4 key risk messages, only 1 component had a response rate less than the threshold of 65%. This component concerned the behavior of prescribing TIRF medicines to opioid tolerant patients with chronic non-cancer pain. The response from prescribers regarding the correct response that TIRF medicines are not prescribed for non-cancer pain has been consistently low for all 3 surveys. While included as part of a key risk message based on FDA request, this question gauges prescriber behavior rather than knowledge. Based on FDA feedback an additional question will be added to the 48-month survey asking prescribers why they feel this is an appropriate use of a TIRF medicine.

In addition, there were four questions about the safe use of TIRF medicines that had a component with an understanding rate below the threshold of 65%. Knowledge that a cancer

patient should not be started on a TIRF medicine and an around-the-clock opioid at the same time was 63.3%. This concept also scored low for pharmacists during this reporting period. The desired response of “false” to the behavior question of instructing patients that, if they stop taking their around -the-clock opioid medicine, they can continue to take their TIRF medicine was selected by 61.0% of prescribers. This concept also scored low in the patient/caregiver KAB survey for this reporting period. Similarly, knowledge that patients should not continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine had a correct response rate of 59.7%. Again, this concept scored low in the patients/caregiver KAB survey. Knowledge that patients are considered opioid-tolerant if taking an equianalgesic dose of another oral opioid one week or longer was selected by 59.0%. For this reporting period, pharmacists also had a similar response for this concept (59.0%).

The consistently high level of prescriber understanding of key risk messages in the 24-month and 36-month surveys indicates that the Education Program for Prescribers and Pharmacists is meeting the goals of the TIRF REMS. Changes will be implemented into the 48-month Prescriber KAB survey based on FDA feedback already received from the 24-month TIRF REMS assessment report.

Based on the data provided in this report the TRIG concludes that the REMS is meeting its established goals. The improvement in knowledge demonstrated by pharmacists and prescribers and the continued high level of awareness of most key risk messages by patients provides evidence that the current tools are effectively communicating the important safety messages to key stakeholders. Based on our analysis of the data for this 36-month assessment, the TRIG is recommending no REMS modifications at this time.

1 BACKGROUND

Opioids remain the mainstay of treatment of moderate to severe pain, but their safe use requires careful consideration of proper patient selection and treatment characteristics in order to mitigate any inherent health risks.

Opioids are formulated as both extended-release and immediate-release products. Extended-release or long acting opioid products are designed to provide extended analgesic activity to control persistent pain.

TIRF medicines and short-acting opioid products have a rapid onset and short duration of action and are designed for the treatment of acute episodes of pain that 'break through' the chronic pain control (breakthrough pain, (BTP). All the TIRF medicines are short-acting fentanyl products.

As with all high-potency opioid analgesics, there are significant potential risks associated with the use and misuse of TIRF medicines, including acute respiratory depression which may lead to death. With appropriate clinical use in opioid-tolerant patients these risks have been shown to be low. However, instances of diversion, overdose and prescribing to opioid-non-tolerant patients have led to serious and, on occasion, fatal, adverse events demonstrating that short-acting fentanyl products can pose a health risk if not used appropriately.

The FDA has determined that a REMS is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The group of Sponsors that are submitting this 36-month REMS include (Cephalon, Inc. [a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.], Depomed, Inc., Galena Biopharma, Inc., Insys Therapeutics Inc., Mallinckrodt Pharmaceuticals, Meda Pharmaceuticals, Mylan, Inc. and Par Pharmaceutical, Inc.) are hereafter referred to as the TIRF Sponsors. The TIRF REMS Access Program is administered by McKesson Specialty Health and RelayHealth. This report is prepared by United BioSource Corporation (UBC).

The TIRF medicines that are the subject of this TIRF REMS are shown in Table 1 below.

Table 1 TIRF Medicines

Product Name (active ingredient)/formulation
NDA 022510, ABSTRAL (fentanyl) sublingual tablets
NDA 020747, ACTIQ (fentanyl citrate) oral transmucosal lozenge and its authorized generic
NDA 021947, FENTORA (fentanyl buccal tablet)
NDA 022569, LAZANDA (fentanyl) nasal spray
NDA 022266, ONSOLIS (fentanyl), buccal soluble film
NDA 202788, SUBSYS (fentanyl sublingual spray)
ANDA 077312, fentanyl citrate oral transmucosal lozenge
ANDA 078907, fentanyl citrate oral transmucosal lozenge

The TIRF REMS Access Program addresses the current requirements set forth by the FDA and provided to TIRF Sponsors. The program will be monitored over time and modified when and where appropriate.

The initial REMS was approved on 28 December 2011 and went live on 12 March 2012. The FDA required an initial report 6 months and 12 months after REMS approval and annually thereafter (Table 2). Reporting periods for each assessment report are described below. To allow for enough time to prepare the report for FDA submission, data cut-off is 60 days prior to the submission date.

Table 2 Assessment Report Periods

Assessment Report	Reporting Period	Submission Date
6-Month	28 December 2011 - 27 April 2012	28 June 2012
12-Month	28 April 2012 - 28 October 2012	28 December 2012
24-Month	29 October 2012 - 28 October 2013	28 December 2013
36-Month	29 October 2013 – 28 October 2014	28 December 2014

2 REMS GOALS

The goals of the TIRF REMS Access Program are to mitigate the risks of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

3 SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS

The TIRF Sponsors are executing the TIRF REMS Access Program to ensure the appropriate use of TIRF medicines and proper patient selection. All stakeholders subject to the TIRF REMS Access Program including patients, prescribers, pharmacies and distributors must be enrolled in the TIRF REMS Access Program, educated on the requirements of the program and required to document that they understand and will abide by the ETASU.

Program materials are provided on the TIRF medicines in addition to product-specific materials. The Education Program and Knowledge Assessment components of the program contain both TIRF medicine class and product-specific components. All program tools, including enrollment

forms, PPAFs, stakeholder letters, and overview documents containing program information specific to the TIRF REMS Access Program, are available through www.TIRFREMSACCESS.com.

The program procedures are monitored for adherence and the TIRF Sponsors will continue to conduct ongoing and retrospective analyses as necessary to comply with all mandates and to maximize the safe use of the TIRF medicines.

3.1 Additional Elements

3.1.1 Medication Guide

The product-specific TIRF Medication Guide should be dispensed with each TIRF medicine prescription. Every TIRF medicine has a unique Medication Guide.

3.1.2 Letters to Healthcare Professionals

A Communication Plan for the TIRF REMS was not required. However, TIRF Sponsors sent materials to targeted stakeholders to support implementation of the TIRF REMS Access Program at the time of program launch. These communications included Dear Healthcare Provider (HCP) and Dear Pharmacy letters, and informed prescribers and authorized pharmacists on the risks associated with the use of TIRF medicines, the procedures and requirements of the TIRF REMS Access Program and means of reporting adverse events.

3.2 Elements To Assure Safe Use

Because of the significant potential health risks associated with prescribing TIRF medicines to opioid non-tolerant patients, it is important that prescribers are aware of the procedures for appropriate patient selection and appropriate dosing and titration. This is achieved by each prescriber's enrollment through a review of the TIRF REMS Access Education Program including the TIRF medicine's Full Prescribing Information, successful completion of the Knowledge Assessment, and completion of the enrollment form.

TIRF medicines are only available through the TIRF REMS Access Program to reduce the risks of inappropriate patient selection and ensure appropriate dosing and administration of TIRF medicines. To ensure that TIRF medicines are only dispensed to appropriate patients, pharmacies that dispense TIRF medicines must be enrolled into the TIRF REMS Access Program. There are different enrollment requirements for outpatient pharmacies (e.g., retail, mail order, institutional outpatient pharmacies that dispense for outpatient use) and inpatient pharmacies (e.g., hospitals that dispense for inpatient use only). For Long-Term Care and Hospice patients whose prescriptions were obtained through an outpatient pharmacy setting, the pharmacy, patient, and prescriber must be enrolled in the TIRF REMS Access Program.

Outpatient pharmacy enrollment requires an authorized pharmacist at the pharmacy to review the TIRF REMS Access Education Program, successfully complete the Knowledge Assessment and submit a completed and signed TIRF REMS Access Program enrollment form. The authorized pharmacist ensures that their Pharmacy Management System (PMS) is able to support communication with the TIRF REMS Access Program using established telecommunication standards. This requires submitting standardized validation test transactions

to validate the system enhancements. The authorized pharmacist is also responsible for educating all pharmacy staff, who participate in dispensing TIRF medicines, on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access Program.

For chain pharmacies, an authorized chain pharmacy representative completes the enrollment process on behalf of all individual store locations associated with that chain. The authorized chain pharmacy representative acknowledges that training has been provided to all pharmacy staff involved in the dispensing of TIRF medicines. Once the TIRF REMS Access Education Program and Knowledge Assessment have been completed, the authorized chain pharmacy representative, on behalf of the chain, is required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access Program requirements by submitting a completed and signed enrollment form.

For inpatient pharmacy enrollment, the authorized pharmacist is required to review the TIRF REMS Access Education Program, successfully complete the Knowledge Assessment, and submit a completed and signed enrollment form on behalf of the pharmacy. The authorized inpatient pharmacist is required to acknowledge that they understand that outpatient pharmacies within their facility must be enrolled separately.

Implementation of the TIRF REMS Access Program for closed system outpatient pharmacies launched on 30 June 2012. Closed system outpatient pharmacies are integrated healthcare systems that dispense for outpatient use but their pharmacy management systems are unable to support the process of electronically transmitting the validation and claim information. To enroll in the TIRF REMS Access Program, the authorized pharmacist must review the TIRF REMS Access Education Program, successfully complete the Knowledge Assessment, and submit a completed and signed enrollment form on behalf of the pharmacy. A list of closed system pharmacies that have been trained must be provided to the TIRF REMS Access Program.

Patients are passively enrolled in the TIRF REMS Access Program when their first prescription is processed by a pharmacy. A completed PPAF should be sent to the TIRF REMS Access Program by the prescriber within 10 working days from the processing date of the patient's first prescription for a TIRF medicine. A maximum of 3 prescriptions are allowed within 10 working days from the date that the patient had their first prescription filled. No further prescriptions are to be dispensed after the 10 working day window until a completed PPAF is received. A patient's HCP can submit a copy of the PPAF to the TIRF REMS Access Program via the Web site, fax, or United States (US) mail.

3.2.1 Prescription Verification

Following initial patient enrollment upon processing of a patient's first TIRF medicine prescription, pharmacies verify for all subsequent prescriptions that both the prescriber and patient are enrolled in the TIRF REMS Access Program and that all REMS requirements are met prior to dispensing. Prescription verification is not required for inpatient use of TIRF medicines.

Specific reasons why a prescription would not meet a REMS edit are described in Table 16.

Non-Closed System Pharmacies

Prescription verification occurs through a model that uses a pharmacy billing claim and engages a switch provider in the validation process.

Upon receipt of a prescription for a TIRF medicine at an enrolled pharmacy, the prescription details are entered into their PMS and a transaction is sent to the TIRF REMS Access Program via a switch provider. If the patient is not enrolled and this is their first prescription, the TIRF REMS Access Program uses the transaction data to automatically transfer patient details into the TIRF REMS Access database for passive enrollment.

For all subsequent prescriptions, the REMS database is then interrogated, via the switch provider, to validate the REMS edits (i.e., confirm that all TIRF REMS Access Program requirements are met).

In the case where a prescription passes all REMS edits, a billing request is then sent to the payer by the switch provider. Once the payer authorizes payment, the switch provider then authorizes the pharmacy to dispense the TIRF medicine as with a normal prescription, returning an authorization number which is captured by the TIRF REMS Access Program.

If the prescription does not pass all REMS edits (e.g., one of the stakeholders was not enrolled), the TIRF REMS Access Program rejects the claim prior to the claim being forwarded to the payer and the pharmacy receives a rejection notice from the switch provider. This automated feedback indicates the reason for rejection, instructs the pharmacist not to dispense the TIRF medicine, and notifies the pharmacist to contact the TIRF REMS Access Program Call Center for further information.

Closed System Outpatient Pharmacies

Upon receipt of a prescription for a TIRF medicine at an enrolled closed system outpatient pharmacy, a pharmacy staff member will contact the TIRF REMS Access Program via phone or fax to provide prescription details for verification. The TIRF REMS Access Program then validates the enrollment status for the patient, prescriber and pharmacy. If the patient is not enrolled, the TIRF REMS Access Program will use this transaction information to automatically transfer patient details into the TIRF REMS Access database for passive enrollment. If all three stakeholders are enrolled (i.e., passes all REMS edits), the closed system outpatient pharmacy is given an authorization number which is captured by the TIRF REMS Access Program. If the prescription does not pass all REMS edits (e.g., one of the stakeholders is not enrolled), the TIRF REMS Access Program will not provide an authorization number and the closed system outpatient pharmacy will receive a rejection notice. This feedback will be provided to the closed system outpatient pharmacy via phone or fax and will include the reason for rejection, information on how the rejection may be resolved and instructions to not dispense the TIRF prescription until resolution is reached.

3.3 Implementation System

The Implementation System and its components are described in the following sections.

3.3.1 Wholesaler/Distribution Enrollment and Fulfillment

Wholesalers/distributors who distribute TIRF medicines must be enrolled in the TIRF REMS Access Program before they are allowed to distribute TIRF medicines.

For the purpose of the TIRF REMS Access Program, the term distributor refers to wholesaler, distributor, and/or chain pharmacy distributor. TIRF medicine distributors received a Dear Distributor Letter describing the TIRF REMS Access Program and the requirements to purchase TIRF medicines from TIRF Sponsors and sell TIRF medicines to pharmacies upon FDA approval of the program. To enroll, the distributor's authorized representative must review the distributor program materials, complete and sign the Distributor Enrollment Form and fax it to the TIRF REMS Access Program. TIRF Sponsors have processes in place to prevent shipping TIRF medicines to any distributor who has not completed and signed the enrollment form.

3.3.2 The TIRF REMS Access Program Compliance [Metric 22]

The TIRF REMS Access Program NCRT was created by the TRIG on 19 October 2012 and is tasked with reviewing reports of suspected non-compliance with the TIRF REMS Access Program requirements. The NCRT is composed of membership from all TRIG sponsors. There are currently 25 individuals across the 8 sponsors; the functional areas or specialties represented by the members include Regulatory, Medical Affairs, REMS Specialist, Legal, Quality and Drug Safety.

TIRF Sponsors monitor prescriber, pharmacy, and wholesaler/distributor activities for compliance with TIRF REMS Access Program requirements. Corrective actions (e.g., re-education, additional monitoring, process revision, stakeholder inactivation) are instituted by the TIRF Sponsors as appropriate if non-compliance is confirmed. The Non-Compliance Plan is described in Section 4.1.4 (Metric 22) and results of non-compliance investigations are included in Section 6 of this report.

3.3.3 TIRF REMS Access Program Call Center

The TIRF REMS Access Program includes a Call Center component. The Call Center is staffed by qualified and trained specialists, who provide TIRF REMS Access Program support to patients, prescribers, pharmacies, and distributors.

4 REMS ASSESSMENT PLAN METHODS

The aim of the TIRF REMS Access Program's evaluation is to assess the effectiveness of the mitigation strategies in meeting the goals of the TIRF REMS Access Program to ensure safe use, proper prescribing, and appropriate distribution of TIRF medicines. Findings from these evaluations are used to identify ways to improve the processes, as needed.

Based on communications between TRIG and the FDA, a revised assessment plan was provided by FDA within the 24-Month Assessment Report Acknowledgement Letter. Due to timing of the revised assessment plan the following metrics are not included in this assessment report, but will be reported in the 48-Month Assessment Report:

Metric Number*	Metric
21.	Report the results of yearly audits of at least 5 randomly selected inpatient hospital pharmacies to assess the performance of the system(s) developed to assure REMS compliance starting in the 48-Month Assessment Report. Provide the number of units of use of TIRFs ordered per inpatient hospital pharmacy audited per 12 month period. These reports are to include: • Verification of training for all pharmacists dispensing TIRF products • Verification that processes such as order sets/protocols are in place to assure compliance with the REMS program • Describe any corrective actions taken for any non-compliance items identified above during the audit, as well as preventative measures that were developed as a result of uncovering these non-compliance events

*As indicated in the Revised Assessment Plan within the 24-Month REMS Assessment Acknowledgement Letter and the revised Supporting Document submitted 10 December 2014.

4.1 Data Sources for REMS Assessments

Data were collected from the following main sources as described in detail below: a) TIRF REMS Access Program utilization statistics (Section 4.1.1), b) dispensing activity for enrolled pharmacies (Section 4.1.2), c) program infrastructure and performance, d) TIRF REMS Access non-compliance plan, e) safety surveillance, f) periodic surveys of patients, HCPs, and pharmacies. All programmed source tables and figures, as well as source data are on file at UBC and available upon request. The individual metrics for each main data source are provided below with a direct link to the results sections of the report.

4.1.1 The TIRF REMS Access Program and Product Utilization Statistics

For the assessment of enrollment, utilization, and discontinuation statistics for prescribers, pharmacies, patients, and distributors, the following metrics were tabulated for the current reporting period and cumulatively.

Metric Number*	Metric
a.	**Patient Enrollment**
1.	Number of unique patients enrolled
2.	Number of patients inactivated
b.	**Prescriber Enrollment**
3.	Number of prescribers enrolled
4.	Number of prescribers that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending
5.	Number of prescribers inactivated
c.	**Pharmacy Enrollment**

Metric Number*	Metric
6	Number of pharmacies enrolled by type (inpatient, chain, independent, closed system; provide identity of closed system entities)
7.	Number of pharmacies that attempted enrollment but whose enrollment is pending >3 months and >6 months along with the specific reasons why their enrollment is pending (stratified by type)
8.	Number of pharmacies inactivated by type (inpatient, chain, independent, closed system)
d.	**Distributor Enrollment**
9.	Number of distributors enrolled
10.	Number of distributors inactivated

*As indicated in the Revised Assessment Plan within the 24-Month REMS Assessment Acknowledgement Letter from FDA and the revised REMS Supporting Document submitted 10 December 2014.

4.1.2 Dispensing Activity for Enrolled Pharmacies

For the assessment of dispensing activity the following metrics were tabulated and stratified by pharmacy type for the current reporting period and cumulatively.

Metric Number*	Metric
11.	Number of prescriptions/transactions authorized; for closed systems, provide the number of prescription/transactions per closed system entity
12.	Number of prescriptions/transactions denied/rejected and the reasons for denial/rejection. Include the number of prescriptions/transactions rejected for safety issues (provide description of safety issues and any interventions or corrective actions taken)
13.	The mean and median amount of time it takes for a prescription that experienced at least one initial REMS-related rejection to be authorized
14.	Number of patients with more than three prescriptions dispensed during the first ten days after patient passive enrollment without a PPAF
15.	Number of prescriptions dispensed after ten days without a PPAF in place

*As indicated in the Revised Assessment Plan within the 24-Month REMS Assessment Acknowledgement Letter from FDA and the revised REMS Supporting Document submitted 10 December 2014.

4.1.3 Program Infrastructure and Performance

The following metrics on program infrastructure performance were collected and summarized for the current reporting period.

Metric Number*	Metric
16.	Number of times a backup system was used to validate a prescription, with reason(s) for each instance (for example, pharmacy level problem, switch problem, or REMS database problem)

Metric Number*	Metric
	clearly defined and described
17.	Number of times unintended system interruptions occurred for each reporting period. Describe the number of stakeholders affected, how the issue was resolved, and steps put into place to minimize the impact of future interruptions
18.	Call center report with • Overall number of contacts • Summary of frequently asked questions • Summary of REMS-related problems reported
19.	Description of corrective actions taken to address program/system problems

*As indicated in the Revised Assessment Plan within the 24-Month REMS Assessment Acknowledgement Letter from FDA and the revised REMS Supporting Document submitted 10 December 2014.

4.1.4 TIRF REMS Access Program Non-Compliance Plan

The TIRF sponsors provide the following data regarding non-compliance in each assessment report (per reporting period).

Metric Number*	Metric
20.	Report the results of yearly audits of at least 3 randomly selected closed pharmacy systems to assess the performance of the system(s) developed to assure REMS compliance. These reports are to include: • Verification of training for all pharmacists dispensing TIRF products • Numbers of prescription authorizations per closed system • Reconciliation of data describing TIRF product prescriptions received by the closed system pharmacy with TIRF product dispensed to patients with a valid enrollment in the TIRF REMS Access program. Data to include the 12 month period preceding the audit date. Include details on how the reconciliation is conducted (e.g., electronic versus manual process). • Describe any corrective actions taken for any non-compliance identified during the audit and corrective actions taken to address non-compliance
22.	Description of number, specialties, and affiliations of the personnel that constitute the Non-Compliance Review Team (NCRT) as well as: • Description of how the NCRT defines a non-compliance event • Description of how non-compliance information is collected and tracked • Criteria and processes the Team uses to make decisions • Summary of decisions the Team has made during the reporting period • How the Team determines when the compliance plan should be modified
23.	Describe each non-compliance event and the corrective action measure taken, as well as the

Metric Number*	Metric
	outcome of the corrective action
24.	Number of TIRF prescriptions dispensed that were written by non-enrolled prescribers and include steps taken to prevent future occurrences
25.	Number of prescriptions dispensed by non-enrolled pharmacies and include steps taken to prevent future occurrences
26.	Number of times a TIRF prescription was dispensed because a pharmacy (closed or open system) was able to bypass REMS edits and if any such events occurred, describe how these events were identified
27.	Number of times a TIRF was prescribed to an opioid non-tolerant individual. Include what was done to minimize such instances; if any such events occurred, describe how these events were identified
28.	Number of instances of inappropriate conversions between TIRF products, as well as any outcome of such an event. If any such events occurred, describe how these events were identified

*As indicated in the Revised Assessment Plan within the 24-Month REMS Assessment Acknowledgement Letter and the revised Supporting Document submitted 10 December 2014.

4.1.4.1 Non-Compliance Monitoring

The TIRF REMS Access Program is in place to ensure the safe and appropriate use of TIRF medications. The goal of the Non-Compliance Plan is to help TRIG identify and investigate deviations from and non-compliance (NC) with TIRF REMS requirements in order to ensure patient safety and continuously improve the program. A confirmed NC event is one for which the information collected through investigation of the potential NC event clearly indicates that a program deviation has occurred and/or evidence of the program goals not being met through stakeholder actions is identified.

The TIRF REMS Access Program routinely monitors stakeholder activity to identify potential incidents of NC events with program requirements. The TIRF REMS Access Program investigates all reports of suspected NC. Routine monitoring of stakeholder activity includes, but is not limited to, the types identified in Table 3. Non-compliance information is collected through standard program reports, spontaneous reports identified via the program's Call Center, vendor/sponsor reported events, outreach to relevant stakeholders to validate data/information and solicit further information, and investigation of the TIRF REMS Access database. The data are tracked through a NC case that is opened on the stakeholder record in the TIRF REMS Access database. Table 3 indicates each defined NC activity and the method of monitoring.

Table 3 Non-Compliance Activity Monitoring

Stakeholder		Scenario
	#	Non-Compliance Activity
Pharmacy	1	Submission of a claim that did not go through the REMS edits. A TIRF medicine was

		dispensed without verifying through the TIRF pharmacy management system that the prescriber is enrolled and active, and that the patient is enrolled or has not been inactivated in the program.
	2	Dispensing activity for enrolled outpatient pharmacies during reporting period not matching distributor shipment data for that pharmacy.
	3	Pharmacy is dispensing TIRF medicine while suspended or deactivated from the TIRF REMS Access program.
	4	[Placeholder for additional scenario if needed]
	5	Authorized Inpatient Pharmacy does not comply with the requirements of the TIRF REMS Access program.
	6	Inpatient Pharmacy dispenses for outpatient use
	7	Submission of inappropriately altered claim to meet TIRF REMS system requirements (e.g. changing prescriber)
Closed System Pharmacy	1	Dispensing prescriptions outside of the closed system authorization process.
Wholesaler/ Distributor	1	Wholesaler/Distributor is suspended or deactivated from the TIRF REMS Access program and is purchasing or distributing TIRF medicines.
	2	Wholesaler/Distributor fills an order for TIRF medicines for a non-enrolled stakeholder.
Prescriber	1	Prescriber is prescribing TIRF medicines while suspended or deactivated from the TIRF REMS Access program.
	2	Prescriber failure to have a complete PPAF on file in a timely manner (5 or more patients enrolled by the prescriber without a complete PPAF on file, with each patient having greater than 10 working days lapse from initial enrollment date).
Patient	1	The Patient receives prescriptions for TIRF medicines from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, or addiction
All Stakeholders	1	ENROLLMENT MONITORING ONLY: Monitor stakeholders who are not enrolled in TIRF and are associated with non-compliance cases.

If a NC event is confirmed, additional investigation is conducted to determine the scope, impact, and root cause of the event. Stakeholders are notified of the investigation via a formal letter from the TIRF REMS Access Program (see section 4.1.4.2. below) and may also be requested to develop a Corrective Action Plan (CAP). All CAPs are reviewed and approved by the NCRT.

The NCRT will determine if the NC Protocol should be modified as the program evolves. Any changes to the plan proposed by the NCRT will be voted upon by the TRIG.

4.1.4.2 Corrective Action Measures

Decisions are made through the NCRT based on the severity of the action as well as the information collected during the investigation. Stakeholders that fail to comply with one or more elements of the TIRF REMS Access Program will be subject to corrective action.

Appropriate corrective actions are determined by the TIRF REMS Access Program according to the severity of the event as defined below:

- Minor - An unintended (e.g., first-time) event. The corrective action typically involves a written notice to the stakeholder and re-education of the program requirements to prevent re-occurrences of the event.
- Moderate – Multiple occurrences of the same event or a series of distinct, unintended events.
- Serious - Continued events after retraining has occurred. This level of offense may result in a suspension from the program and possible deactivation.

Affected stakeholders are provided written notification of all confirmed NC events. Corrective actions for confirmed events may include a Notice, Warning, Suspension, or Deactivation letter (See Table 4). If deemed necessary, temporary suspension of a prescriber, pharmacist or distributor from the TIRF REMS Access Program may be warranted, prohibiting them from prescribing, dispensing or distributing TIRF medicines for a certain period of time. The most severe consequence of a NC event is deactivation, resulting in the stakeholder not being able to receive/prescribe/dispense/distribute TIRF medicines and is applicable to all stakeholders including patients.

Formal notifications of non-compliance are sent by the TIRF REMS Access Program to the applicable prescriber, pharmacy, and/or distributor whereas notices for patient non-compliance events are sent to their prescriber. Copies of notices sent to an individual chain outpatient pharmacy store or closed system pharmacy store are also sent to the chain outpatient or closed system pharmacy's headquarters.

Table 4 Corrective Action Guideline

Event Classification	Description
Notices	• Patient notices will be sent to a patient's prescriber • Minor violations that demonstrate a misunderstanding of the program requirements • Notices are intended to re-educate stakeholders • 2 Notices in 60 days = Review by Non-Compliance Review Team to determine if escalation to Warning is warranted
Warnings	• 2 Warnings in 60 days = Review by Non-Compliance Review Team to determine if escalation to Suspension is warranted • >1 Warning in >60 days = Case-by-Case review for Suspension

Event Classification	Description
Suspension	• Temporary suspension from the program • A suspended pharmacy or distributor may keep existing TIRF inventory but may not purchase or acquire additional TIRF medicines • Pharmacies may not dispense TIRF medicines from existing inventory and distributors may not sell/distribute TIRF medicines during suspension • If the pharmacy or distributor is part of a larger entity that entity will be notified of the suspension • 1 Warning or 2 Notices while Suspended = Review by Non-Compliance Review Team to determine if escalation to Deactivation is warranted • 2 Suspensions Within a 12-Month Period = Review by Non-Compliance Review Team to determine if a Deactivation is warranted
Deactivation	• Deactivation may result from multiple failures to comply with the program elements and/or a non-compliance event for which there is no feasible corrective action • Bars stakeholder from providing TIRF medicines for their patients • Pharmacies and distributors must return all existing TIRF medicine • Patient deactivation will be sent to a patient's prescriber. Patients may only be reinstated into the program by a request from their prescriber

4.1.5 Safety Surveillance

The following safety surveillance data were collected. Reporting periods for each type of data were modified based on timing of availability of data.

Metric Number*	Metric
29.	TIRF Sponsors will process adverse event reports related to their specific products and report to the FDA according to current regulations outlined in 21 CFR 314.80 and the sponsor's respective Standard Operating Procedures
30.	TIRF Sponsors will produce one comprehensive report that presents spontaneous adverse event data from all sponsors of the TIRF REMS Access program, as well as data from other databases (characteristics of which are described below). This report will focus on four categories of adverse events of interest: addiction, overdose, death, and pediatric exposures. This report should include the following: • Line listings under each category of adverse events of interest as listed above • Line listings should provide at a minimum the following information: o Identifying case number o Age and Gender of the patient o Date of the event as well as of the report o The Preferred Terms o Indication of TIRF use o Duration of TIRF therapy

Metric Number*	Metric
	○ Concomitant medications ○ Event Outcome • Other metrics of interest include: ○ Number of event reports in each event category of interest ○ Counts of adverse events related to inappropriate conversions between TIRF products ○ Counts of adverse events related to accidental and unintentional exposures ○ Counts of adverse events that are associated with use of TIRF medicines in non-opioid tolerant patients • Duplicate cases are identified and eliminated • Case reports with adverse events in multiple categories will be listed in each category of interest, and will be noted as such • For each adverse event category, an overall summary analysis of the cases will be provided addressing the root cause(s) of the events • Rate of each adverse event of interest will be calculated using two distinct denominators: the number of prescriptions for TIRF products and the number of patients receiving a TIRF product throughout the reporting interval. Trends and changes in the rates of these events will be compared year-to-year
31.	Surveillance data focusing on events of addiction, overdose, death, and pediatric cases should also be drawn from the databases that are listed below. Conclusions regarding these data should be included in and inform the overall conclusions in the summary report referred to in Metric 30 directly above: • Non-medical use of prescription drugs • Surveys conducted at substance abuse treatment programs • College surveys • Poison control center data • Impaired health care workers • Drug-related hospital emergency department visits • Drug-related deaths • Other databases as relevant

*As indicated in the Revised Assessment Plan within the 24-Month REMS Assessment Acknowledgement Letter and the revised Supporting Document submitted 10 December 2014.

4.1.6 Periodic Surveys of Patients, Prescribers, and Pharmacies

Prescribers', pharmacists', and patients' understanding regarding the appropriate use of TIRF medicines and TIRF REMS Access Program requirements are evaluated through KAB surveys. The surveys are administered to selected prescribers, pharmacies, and patients.

5 RESULTS

5.1 REMS Program Utilization

Described in this section are the total numbers of all enrolled stakeholders (prescribers, patients, pharmacies, and distributors), as well as stakeholder inactivations, dispensing activities, and barriers or delays in patient access.

5.1.1 Patient Enrollment [Metric 1 and 2]

During the current reporting period, there were 9,744 newly enrolled patients (Table 5). Because patients are passively enrolled with their first prescription there is no patient re-enrollment, but prescribers are required to renew PPAFs with patients every 2 years. By the design of the program, a patient enrollment status will never change to inactivated.

Table 5 Patient Enrollment

Parameter	Current Reporting Period 29OCT2013 to 28OCT2014 Number of Newly Enrolled Patients N (%)	Cumulative[a,b] 28DEC2011 to 28OCT2014 Total Number of Enrolled Patients N (%)
Total Number of Enrolled Patients	9,744[a]	29,222[b,c]

[a] An enrolled patient is a patient who has received at least one prescription for a TIRF prescription.

[b] Includes patients that transitioned into the TIRF REMS Access Program from other individual REMS programs.

[c] Cumulative patients from the end of prior period may differ from last period's report due to reconciliation of duplicate patients.

5.1.2 Prescriber Enrollment and Inactivations [Metric 3, 4, 5]

Cumulatively there have been 12,749 prescribers who have successfully completed enrollment in the program. At the end of this reporting period there are 7,992 prescribers who are currently enrolled. This includes 2,027 newly enrolled prescribers, 3,089 prescribers who re-enrolled and 2,876 who remain active from a previous period (Table 6). Table 7 shows those prescribers who have been inactivated.

Table 6 Prescriber Enrollment

Parameter	Current Reporting Period[a] 29OCT2013 to 28OCT2014 N (%)
Number of Prescribers with Enrollment Activity In This Reporting Period	5,116
Number of Newly Enrolled Prescribers	2,027 (39.6%)
Number of Re-Enrolled Prescribers	3,089 (60.4%)
Number of Prescribers Who Remain Enrolled from Previous Reporting Periods	2,876
Total Number of Prescribers Enrolled as of the End of This Reporting Period	7,992
Cumulative Number of Prescribers Ever Enrolled[b,c]	12,749

[a] Percentages are based on the total number (N) of enrolled prescribers

[b] Cumulative is defined as sum of all reporting periods.

[c] Number includes prescribers who transitioned into the TIRF REMS Access Program

A total of 4,731 prescribers were inactivated at some point during the current reporting period, and the majority of these (4,658; 98.5%) were due to expiration of enrollment. It should be noted that a prescriber is required to enroll every 2 years within the TIRF REMS Access Program. Of those 4,658 prescribers whose enrollment expired at some point during the current reporting period, 3,390 (72.8%) of these prescribers' statuses remained expired at the end of the reporting period (Table 7). In total, there were 4,760 prescribers who remained inactivated at the end of the reporting period.

Table 7 Prescriber Inactivations

Parameter	Current Reporting Period[a] 29OCT2013 to 28OCT2014 N (%)
Number of Prescribers Who Became Inactivated During this Reporting Period	4,731
Reason(s) For Inactivation[b]	
Deceased	2 (<0.1%)
Program Opt-Out	61 (1.3%)
Non Compliant[c]	4 (0.1%)

Parameter	Current Reporting Period[a] 29OCT2013 to 28OCT2014
	N (%)
Suspended	7 (0.1%)
Enrollment Expired[d]	4,658 (98.5%)
Enrollment remained expired at end of period	3,390 (72.8%)
Number of Prescribers Inactivated in This Time Period who Remain Inactivated as of the End of this Reporting Period	3,452
Number of Prescribers Who Were Inactivated in a Previous Reporting Period and Remain Inactive as of the End of This Reporting Period	1,308
Total Number of Prescribers Inactivated as of the End of this Reporting Period	4,760
Cumulative Number of Prescribers Who Have Ever Been Inactivated[e]	6,635

[a] Prescribers whose status is 'inactive' at least once during the reporting period.

[b] Percentages are based on the total number (N) of inactivated prescribers. A prescriber may have more than one reason for inactivation.

[c] Prescribers may be included as both "non-compliant" and "suspended" since before becoming inactivated for non-compliance, prescribers go through a suspension period.

[d] Prescribers whose status is 'Inactive-Expired' at any time during the reporting period.

[e] Cumulative is defined as sum of all reporting periods.

During the current reporting period, there were 71 prescribers who attempted enrollment but whose enrollment was pending 3 to 6 months later. A total of 265 prescribers were pending enrollment for more than 6 months. Prescribers may have attempted enrollment and become pending in another reporting period.

For prescribers pending enrollment for 3 to 6 months, the most frequent reasons were no attestation (81.7%), training not complete (63.4%), and knowledge assessment failure on the first attempt (16.9%). For prescribers pending enrollment for more than 6 months, the most frequent reasons were similar and included no attestation (74.3%), training not complete (72.8%), and knowledge assessment failure on the first attempt (10.2%).

The number of prescribers that attempted enrollment but are still pending enrollment for 3 to 6 months or more than 6 months, and the reasons for pending enrollment are shown in Table 8.

Table 8 Prescribers Pending Enrollment

Parameter	Current Reporting Period[a] 29OCT2013 to 28OCT2014	
	Prescribers Pending Enrollment ≥3 – 6 Months[b]	**Prescribers Pending Enrollment >6 Months[b]**
Prescribers Who Attempted Enrollment but are Still Pending Enrollment[c]	71	265
Reasons for Pending Enrollment		
Assessment Failure - Sixth Attempt	1 (1.4%)	0
Invalid DEA	8 (11.3%)	11 (4.2%)
Invalid NPI	1 (1.4%)	12 (4.5%)
Knowledge Assessment Failure - Fifth Attempt	0	1 (0.4%)
Knowledge Assessment Failure - First Attempt	12 (16.9%)	27 (10.2%)
Knowledge Assessment Failure - Third Attempt	2 (2.8%)	4 (1.5%)
Missing Address – City	0	3 (1.1%)
Missing Address – State	0	3 (1.1%)
Missing Address – Street	0	3 (1.1%)
Missing Address – Zip	0	3 (1.1%)
Missing DEA Number	0	6 (2.3%)
Missing Email	1 (1.4%)	7 (2.6%)
Missing Fax Number	0	2 (0.8%)
Missing NPI Number	4 (5.6%)	9 (3.4%)
Missing Phone Number	0	3 (1.1%)
Missing Physician Signature Date	3 (4.2%)	17 (6.4%)
Missing Preferred Method of Contact	0	2 (0.8%)
Missing Signature	3 (4.2%)	17 (6.4%)
Missing Site Name	0	3 (1.1%)
Missing State License Number	3 (4.2%)	7 (2.6%)
No Attestation	58 (81.7%)	197 (74.3%)
Pending Enrollment Intake	1 (1.4%)	15 (5.7%)
Provided DEA does not have Correct Schedule for this Drug	5 (7%)	18 (6.8%)
Training Access Suspended	1 (1.4%)	0
Training Not Complete	45 (63.4%)	193 (72.8%)

[a] Reflects the total number of prescribers pending enrollment in the current reporting period. Prescribers may have attempted enrollment and become pending in another reporting period.

[b] Percentages are based on the total number (N) of prescribers attempting enrollment. Percentages may not add to 100% because a single prescriber may be pending enrollment for more than one reason

[c] Prescribers may be pending enrollment for more than one reason.

5.1.3 Pharmacy Enrollment, Inactivation, and Education [Metric 6, 7, 8]

There were a total of 16,102 pharmacies newly enrolled or re-enrolled in this reporting period. Of the 1,585 (9.8%) pharmacies that newly enrolled in the TIRF REMS Access Program, 788 were chain pharmacy stores (subset of 4 chain pharmacy headquarters), 588 were independent outpatient pharmacies, 182 were inpatient pharmacies, and 23 were closed system pharmacy locations. The 23 closed system pharmacies are represented by 7 closed system entities (See Section 5.1.5.). A total of 14,517 (90.2%) pharmacies re-enrolled; 11,138 were chain pharmacy stores (under 48 chain pharmacy headquarters), 2,638 were independent outpatient pharmacies, 472 were inpatient pharmacies, and 215 were closed system pharmacy locations (Table 9).

Table 9 Pharmacy Enrollment

Parameter	Current Reporting Period[a,b] 29OCT2013 to 28OCT2014		
	Non-Closed System Pharmacies N (%)	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Total Number of Pharmacies with Enrollment Activity in this Reporting Period	15,858	244	16,102
Total Number of Newly Enrolled Pharmacies	1,562 (9.8%)	23 (9.4%)	1,585 (9.8%)
Inpatient Pharmacies	182 (11.7%)	N/A	182 (11.5%)
Chain Pharmacy Headquarters	4 (0.3%)	N/A	4 (0.3%)
Chain Pharmacy Stores	788 (50.4%)	N/A	788 (49.7%)
Independent Outpatient Pharmacies	588 (37.6%)	N/A	588 (37.1%)
Closed System Headquarters	N/A	0	0
Closed System Pharmacies	N/A	23 (100.0%)	23 (1.5%)
Total Number of Re-Enrolled Pharmacies	14,296 (90.2%)	221 (90.6%)	14,517 (90.2%)
Inpatient Pharmacies	472 (3.3%)	N/A	472 (3.3%)
Chain Pharmacy Headquarters	48 (0.3%)	N/A	48 (0.3%)
Chain Pharmacy Stores	11,138 (77.9%)	N/A	11,138 (76.7%)
Independent Outpatient Pharmacies	2,638 (18.5%)	N/A	2,638 (18.2%)
Closed System Headquarters	N/A	6 (2.7%)	6 (<0.1%)
Closed System Pharmacies	N/A	215 (97.3%)	215 (1.5%)
Number of Pharmacies that Remain Enrolled from a Previous Reporting Period	21,671	2	21,673

Parameter	Current Reporting Period[a,b] 29OCT2013 to 28OCT2014		
	Non-Closed System Pharmacies N (%)	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Inpatient Pharmacies	196 (0.9%)	N/A	196 (0.9%)
Chain Pharmacy Headquarters	26 (0.1%)	N/A	26 (0.1%)
Chain Pharmacy Stores	20,357 (93.9%)	N/A	20,357 (93.9%)
Independent Outpatient Pharmacies	1,092 (5.0%)	N/A	1,092 (5.0%)
Closed System Headquarters	N/A	1 (50.0%)	1 (<0.1%)
Closed System Pharmacies	N/A	1 (50.0%)	1 (<0.1%)
Total Number of Pharmacies Enrolled as of the End of this Reporting Period	37,529	246	37,775
Inpatient Pharmacies	850 (2.3%)	N/A	850 (2.3%)
Chain Pharmacy Headquarters	78 (0.2%)	N/A	78 (0.2%)
Chain Pharmacy Stores	32,283 (86.0%)	N/A	32,283 (85.5%)
Independent Outpatient Pharmacies	4,318 (11.5%)	N/A	4,318 (11.4%)
Closed System Headquarters	N/A	7 (2.8%)	7 (<0.1%)
Closed System Pharmacies	N/A	239 (97.2%)	239 (0.6%)
Cumulative Number of Pharmacies Ever Enrolled	41,303	358	41,661
Inpatient Pharmacies	1,083 (2.6%)	N/A	1,083 (2.6%)
Chain Pharmacy Headquarters	90 (0.2%)	N/A	90 (0.2%)
Chain Pharmacy Stores	34,477 (83.5%)	N/A	34,477 (82.8%)
Independent Outpatient Pharmacies	5,653 (13.7%)	N/A	5,653 (13.6%)
Closed System Headquarters	N/A	7 (2.0%)	7 (<0.1%)
Closed System Pharmacies	N/A	351 (98.0%)	351 (0.8%)

[a] Percentages are based on the total number (N) of pharmacies with enrollment activity in this reporting period for the reporting period.

[b] Pharmacies that are enrolled within this reporting period and were still enrolled at the end of the reporting period.

[c] Cumulative number of pharmacies from the end of prior period may differ from last period's report due to reconciliation of duplicate records.

As shown in Table 10, there were 5,040 total pharmacies inactivated at least once during the current reporting period including 4,873 non-closed system pharmacies and 167 closed system pharmacies. The non-closed system pharmacies included 2,928 (60.1%) chain pharmacy stores (subset of 18 chain pharmacy headquarters), 1,609 (33.0%) independent outpatient pharmacies, and 318 (6.5%) inpatient pharmacies.

The reason for most pharmacy inactivations was enrollment expired, which was 88.9% of the inactivated chain pharmacy headquarters and at least 93.3% among inactivated pharmacies in the remaining pharmacy categories.

Table 10 Pharmacy Inactivations

	Current Reporting Period[a] 29OCT2013 to 28OCT2014		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Number of Pharmacies that Became Inactivated During this Reporting Period	4,873	167	5,040
Inpatient Pharmacies	318 (6.5%)	N/A	318 (6.3%)
Chain Pharmacy Headquarters	18 (0.4%)	N/A	18 (0.4%)
Chain Pharmacy Stores	2,928 (60.1%)	N/A	2,928 (58.1%)
Independent Outpatient Pharmacies	1,609 (33.0%)	N/A	1,609 (31.9%)
Closed System Pharmacies	N/A	167 (100.0%)	167 (3.3%)
Reason(s) for Inpatient Pharmacy Inactivation[b]			
Program Opt-Out	6 (1.9%)	N/A	6 (1.9%)
Enrollment Expired[c]	312 (98.1%)	N/A	312 (98.1%)
Enrollment remained expired at end of period	215 (68.9%)	N/A	215 (68.9%)
Reason(s) for Chain Pharmacy Headquarters Inactivation[d]			
Program Opt-Out	2 (11.1%)	N/A	2 (11.1%)
Enrollment Expired[c]	16 (88.9%)	N/A	16 (88.9%)
Enrollment remained expired at end of period	9 (56.3%)	N/A	9 (56.3%)

Parameter	Current Reporting Period[a] 29OCT2013 to 28OCT2014		
	Non-Closed System Pharmacies N (%)	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Reason(s) for Chain Pharmacy Store Inactivation[d]			
Program Opt-Out	195 (6.7%)	N/A	195 (6.7%)
Enrollment Expired[c]	2,733 (93.3%)	N/A	2,733 (93.3%)
Enrollment remained expired at end of period	1,470 (53.8%)	N/A	1,470 (53.8%)
Reason(s) for Independent Outpatient Pharmacy Inactivation[e]			
Program Opt-Out	35 (2.2%)	N/A	35 (2.2%)
Enrollment Expired[c]	1,574 (97.8%)	N/A	1,574 (97.8%)
Enrollment remained expired at end of period	1,107 (70.3%)	N/A	1,107 (70.3%)
Reason(s) For Closed System Pharmacy Inactivation[f]			
Enrollment Expired[c]	N/A	167 (100.0%)	167 (100.0%)
Enrollment remained expired at end of period	N/A	112 (67.1%)	112 (67.1%)
Numbers of Pharmacies Inactivated in This Time Period that Remain Inactivated as of the End of this Reporting Period	3,021	112	3,133
Inpatient Pharmacies	220 (7.3%)	N/A	220 (7.0%)
Chain Pharmacy Headquarters	11 (0.4%)	N/A	11 (0.4%)
Chain Pharmacy Stores	1,649 (54.6%)	N/A	1,649 (52.6%)
Independent Outpatient Pharmacies	1,141 (37.8%)	N/A	1,141 (36.4%)
Closed System Pharmacies	N/A	112 (100.0%)	112 (3.6%)
Total Number of Pharmacies Inactivated as of the End of This Reporting Period	3,774	112	3,886
Inpatient Pharmacies	233 (6.2%)	N/A	233 (6.0%)
Chain Pharmacy Headquarters	12 (0.3%)	N/A	12 (0.3%)
Chain Pharmacy Stores	2,194 (58.1%)	N/A	2,194 (56.5%)
Independent Outpatient Pharmacies	1,335 (35.4%)	N/A	1,335 (34.4%)
Closed System Pharmacies	N/A	112 (100.0%)	112 (2.9%)
Cumulative Number of Pharmacies Ever Inactivated[g]	7,371	167	7,538
Inpatient Pharmacies	341 (4.6%)	N/A	341 (4.5%)

Parameter	Current Reporting Period[a] 29OCT2013 to 28OCT2014		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	Total Pharmacies N (%)
Chain Pharmacy Headquarters	20 (0.3%)	N/A	20 (0.3%)
Chain Pharmacy Stores	5,091 (69.1%)	N/A	5,091 (67.5%)
Independent Outpatient Pharmacies	1,919 (26.0%)	N/A	1,919 (25.5%)
Closed System Pharmacies	N/A	167 (100.0%)	167 (2.2%)

[a] Pharmacies with 'inactive' status at least once during the reporting period.

[b] Percentages are based on the total number (N) of inactivated inpatient pharmacies. An inpatient pharmacy may have more than one reason for inactivation.

[c] Pharmacies whose status is 'Inactive-Expired' at any time during the enrollment period.

[d] Percentages are based on the total number (N) of inactivated chain pharmacy headquarters or chain pharmacy stores. A chain pharmacy headquarters or chain pharmacy store may have more than one reason for inactivation.

[e] Percentages are based on the total number (N) of inactivated independent outpatient pharmacy stores. An independent outpatient pharmacy store may have more than one reason for inactivation.

[f] Percentages are based on the total number (N) of inactivated closed system pharmacies. A closed system pharmacy may have more than one reason for inactivation.

[g] Cumulative is sum of all reporting period totals.

During the current reporting period, there were 50 pharmacies that attempted enrollment but enrollment was pending 3 to 6 months later. As of the end of the reporting period, there were a total of 229 pharmacies pending enrollment for 6 months or longer. Pharmacies may have attempted enrollment and become pending in another reporting period.

For pharmacies pending enrollment for 3 to 6 months, the most frequent reasons were pending test transaction verification (56.0%), no attestation (42.0%), and training not complete (36.0%).

For pharmacies pending enrollment for 6 months or longer, the most frequent reasons were similar and included pending test transaction verification (52.4%), no attestation (45.4%), and training not complete (34.9%).

The number of pharmacies that attempted enrollment but are still pending enrollment for 3 to 6 months or longer than 6 months, and the reasons for pending enrollment are shown in Table 11.

Table 11 Pharmacies Pending Enrollment

Parameter	Current Reporting Period[a] 29OCT2013 to 28OCT2014					
	Pharmacies Pending Enrollment ≥3 - 6Months[b]			Pharmacies Pending Enrollment: >6 Months[b]		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	Total Pharmacies N (%)	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	Total Pharmacies N (%)
Pharmacies that Attempted Enrollment but are Still Pending Enrollment[c]	50	0	50	229	0	229
Reasons for Pending Enrollment						
Invalid DEA	0	0	0	4 (1.7%)	0	4 (1.7%)
Invalid NCPDP	0	0	0	3 (1.3%)	0	3 (1.3%)
Invalid NPI	0	0	0	2 (0.9%)	0	2 (0.9%)
Knowledge Assessment Failure - First Attempt	1 (2.0%)	0	1 (2.0%)	7 (3.1%)	0	7 (3.1%)
Knowledge Assessment Failure - Third Attempt	0	0	0	2 (0.9%)	0	2 (0.9%)
Missing Address – City	0	0	0	1 (0.4%)	0	1 (0.4%)
Missing Address – State	0	0	0	1 (0.4%)	0	1 (0.4%)
Missing Address – Street	0	0	0	1 (0.4%)	0	1 (0.4%)
Missing Pharmacist Signature Date	0	0	0	3 (1.3%)	0	3 (1.3%)
Missing Signature	0	0	0	3 (1.3%)	0	3 (1.3%)
No Attestation	21 (42.0%)	0	21 (42.0%)	104 (45.4%)	0	104 (45.4%)
Pending Enrollment Intake	3 (6.0%)	0	3 (6.0%)	1 (0.4%)	0	1 (0.4%)
Pending Test Transaction Verification	28 (56.0%)	0	28 (56.0%)	120 (52.4%)	0	120 (52.4%)
Training Not Complete	18 (36.0%)	0	18 (36.0%)	80 (34.9%)	0	80 (34.9%)

[a] Reflects the total number of pharmacies pending enrollment in the current reporting period. Pharmacies may have attempted enrollment and became pending in another reporting period.

[b] Percentages are based on the total number (N) of pharmacies attempting enrollment. Percentages may not add up to 100% because a single pharmacy may be pending enrollment for more than one reason.

[c] Pharmacies may be pending enrollment for more than one reason.

5.1.4 Wholesaler/Distributor Enrollment [Metric 9 and 10]

During the current reporting period, 1 (4.5%) wholesaler/distributor newly enrolled in the REMS program and 22 (95.5%) re-enrolled (Table 12).

There were 10 wholesalers/distributors inactivated during the current reporting period because the enrollment expired and 8 had not re-enrolled by the end of the reporting period (Table 13).

Table 12 Distributor Enrollment

	Current Reporting Period[a] 29OCT2013 to 28OCT2014
Parameter	**N (%)**
Number of Distributors with Enrollment Activity in This Reporting Period	22
Number of Newly Enrolled Distributors	1 (4.5%)
Number of Re-Enrolled Distributors	21 (95.5%)
Number of Distributors that Remain Enrolled from Previous Reporting Periods	13
Total Number of Distributors Enrolled as of the End of the Reporting Period	35
Cumulative Number of Distributors Ever Enrolled[c]	45

[a] Percentages are based on the total number (N) for the relevant Distributors for the period.

[b] Includes Distributors that transitioned into the TIRF REMS Access Program from other individual REMS programs.

[c] Cumulative Distributors from the end of prior period may differ from last period's report due to reconciliation of duplicate Distributors.

Table 13 Distributor Inactivations

	Current Reporting Period[a] 29OCT2013 to 28OCT2014
Parameter	**N (%)**
Number of Distributors that Became Inactivated in This Reporting Period	10
Reason(s) for Distributor Inactivation	

	Current Reporting Period[a] 29OCT2013 to 28OCT2014
Parameter	**N (%)**
Enrollment Expired[c]	10 (100.0%)
Enrollment remained expired at end of period	8 (80.0%)
Number of Distributors that Remain Inactivated From Previous Reporting Periods	2
Total Number of Distributors Inactivated as of the End of the Reporting Period	10
Cumulative Number of Distributors Ever Inactivated[c]	14

[a] Distributors with 'inactive' status at least once during the reporting period.

[b] Distributors whose status is 'Inactive-Expired' at any time during the enrollment period.

[c] Cumulative is sum of all reporting period totals.

5.1.5 Dispensing Activity [Metric 11, 12, 13,]

A total of 159,560 prescriptions were adjudicated for safety by the TIRF REMS Access Program in the current reporting period including 158,612 prescriptions from non-closed system pharmacies and 948 from closed system pharmacies (Table 14). Of the total prescriptions, 90.9% were subsequently approved for dispensing without encountering any REMS-related rejections (i.e., were authorized for dispensing by insurance or cash bin).

Table 14 Prescriptions from Outpatient Pharmacies That Did Not Encounter Any REMS-Related Rejections Prior to Being Authorized for Dispensing

	Current Reporting Period[a,b] 29OCT2013 to 28OCT2014			Cumulative[a,b,c] 28DEC2011 to 28OCT2014		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**
Number of Unique Prescriptions Presented for Dispensing	158,612	948	159,560	407,228	2,580	409,808
Total Number of Unique Prescriptions That Did Not Encounter Any REMS-Related Rejections Prior to Being Authorized for Dispensing	144,364 (91.0%)	720 (75.9%)	145,084 (90.9%)	356,302 (87.5%)	2,018 (78.2%)	358,320 (87.4%)
Independent Pharmacies	104,019 (65.6%)	N/A	104,019 (65.2%)	223,352 (54.8%)	N/A	223,352 (54.5%)
Chain Pharmacies	40,345 (25.4%)	N/A	40,345 (25.3%)	132,950 (32.6%)	N/A	132,950 (32.4%)
Closed System Pharmacies	N/A	720 (75.9%)	720 (0.5%)	N/A	2,018 (78.2%)	2,018 (0.5%)

[a] Prescriptions successfully adjudicated for safety (i.e., successful REMS edit).and authorized for dispensing by insurance or cash bin (bin number).

[b] Percentages are based on the total number (N) of unique prescriptions that never encountered a REMS-related rejection for the reporting period.

[c] Includes authorizations from all pharmacies that were enrolled in the TIRF REMS Access Program at any time from inception of the program.

Of the 159,560 unique prescriptions presented for dispensing during the current reporting period, 3,738 prescriptions encountered at least one REMS-related rejection prior to being authorized for dispensing from outpatient pharmacies. There were a total of 10,738 prescriptions that encountered at least one REMS-related rejection and were never authorized for dispensing. Percentages for all rejection reasons may not equal 100% as a prescription may be rejected for multiple reasons.

The most frequent rejection reasons for independent pharmacies (n=2,811) were PPAF incomplete (33.7%), PPAF terminated (23.1%), zip code missing (21.3%), and PPAF expired (19.8%).

The most frequent rejection reasons for chain pharmacies (n=917) were PPAF terminated (42.4%), PPAF expired (37.8%), PPAF incomplete (23.2%), and Prescriber Identification (ID) not registered (17.8%).

The most frequent rejection reasons for closed system pharmacies (n=10) were PPAF terminated (50.0%), PPAF incomplete (50.0%), and PPAF expired (30.0%).

Upon receiving an inbound call from a pharmacy provider, the TIRF REMS Access Program Call Center Service Representative (CSR) works to resolve the rejected transaction and to provide instructions on the corrective action needed to successfully process the transaction. Corrective action includes outreach and education to remedy rejected transaction processing.

Table 15 presents the results for the prescriptions that encountered at least one REMS-related rejection prior to being authorized for dispensing from outpatient pharmacies.

Table 15 Prescriptions from Outpatient Pharmacies That Encountered at Least One REMS-Related Rejection Prior to Being Authorized for Dispensing

	Current Reporting Period[a,b] 29OCT2013 to 28OCT2014			Cumulative[a,b,c] 28DEC2011 to 28OCT2014		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**
Number of Unique Prescriptions Presented for Dispensing	158,612	948	159,560	407,228	2,580	409,808
Total Number of Unique Prescriptions that encountered At Least One Initial REMS-Related Rejection Prior to being Authorized for Dispensing	3,728 (2.4%)	10 (1.1%)	3,738 (2.3%)	16,978 (4.2%)	57 (2.2%)	17,035 (4.2%)
Independent Pharmacies	2,811 (1.8%)	N/A	2,811 (1.8%)	12,311 (3.0%)	N/A	12,311 (3.0%)
Chain Pharmacies	917 (0.6%)	N/A	917 (0.6%)	4,667 (1.1%)	N/A	4,667 (1.1%)
Closed System Pharmacies	N/A	10 (1.1%)	10 (<0.1%)	N/A	57 (2.2%)	57 (<0.1%)
Independent Pharmacies						
Reason(s) for Rejection[d]						
Zip Code Missing	598 (21.3%)			6,253 (50.8%)		
PPAF Incomplete	948 (33.7%)			3,366 (27.3%)		
Prescriber last name did not match registered	273 (9.7%)			1,691 (13.7%)		
Prescriber ID not registered	295 (10.5%)			1,413 (11.5%)		
PPAF terminated	650 (23.1%)			772 (6.3%)		
PPAF Expired	557 (19.8%)			562 (4.6%)		
Prescriber is terminated	96 (3.4%)			203 (1.6%)		
Last Name and DOB Missing	44 (1.6%)			194 (1.6%)		

	Current Reporting Period[a,b] 29OCT2013 to 28OCT2014			Cumulative[a,b,c] 28DEC2011 to 28OCT2014		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**
Pharmacy terminated	19 (0.7%)			108 (0.9%)		
Prescriber ID not submitted	33 (1.2%)			99 (0.8%)		
First Name Missing	22 (0.8%)			61 (0.5%)		
First Name, Last Name, and Zip Code Missing	1 (<0.1%)			24 (0.2%)		
Prescriber Terminated and Last Name Mismatch	9 (0.3%)			21 (0.2%)		
DOB Missing	3 (0.1%)			18 (0.1%)		
Zip Code and Last Name	0			13 (0.1%)		
First Name and Last Name Missing	0			9 (0.1%)		
DOB and Zip Code Missing	1 (<0.1%)			8 (0.1%)		
Last Name Missing	0			2 (<0.1%)		
Database Failure - System Unavailable due to maintenance	0			1 (<0.1%)		
First Name, Last Name and DOB Missing	0			1 (<0.1%)		
First Name, Last Name, Zip Code, and DOB Missing	0			1 (<0.1%)		
Multi-Match - two or more patient match on same criteria	1 (<0.1%)			1 (<0.1%)		
Chain Pharmacies						
Reason(s) for Rejection[d]						
PPAF Incomplete	213 (23.2%)			2,102 (45.0%)		
Prescriber ID not registered	163 (17.8%)			970 (20.8%)		

	Current Reporting Period[a,b] 29OCT2013 to 28OCT2014			Cumulative[a,b,c] 28DEC2011 to 28OCT2014		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**
Zip Code Missing	32 (3.5%)			820 (17.6%)		
PPAF terminated	389 (42.4%)			466 (10.0%)		
Prescriber last name did not match registered	55 (6.0%)			377 (8.1%)		
PPAF Expired	347 (37.8%)			349 (7.5%)		
Prescriber is terminated	36 (3.9%)			74 (1.6%)		
First Name Missing	3 (0.3%)			47 (1.0%)		
Last Name and DOB Missing	7 (0.8%)			32 (0.7%)		
Pharmacy terminated	6 (0.7%)			20 (0.4%)		
Prescriber ID not submitted	2 (0.2%)			17 (0.4%)		
First Name and Last Name Missing	0			7 (0.1%)		
DOB Missing	0			6 (0.1%)		
First Name, Last Name, and Zip Code Missing	0			6 (0.1%)		
Multi-Match - two or more patient match on same criteria	0			3 (0.1%)		
Prescriber Terminated and Last Name Mismatch	2 (0.2%)			3 (0.1%)		
First Name, Last Name and DOB Missing	0			2 (<0.1%)		
First Name, Last Name, Zip Code, and DOB Missing	0			2 (<0.1%)		
Pharmacy not Registered	0			2 (<0.1%)		
DOB and Zip Code Missing	0			1 (<0.1%)		
Database Failure - System unavailable due to system maintenance	0			1 (<0.1%)		

	Current Reporting Period[a,b] 29OCT2013 to 28OCT2014			Cumulative[a,b,c] 28DEC2011 to 28OCT2014		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**
First Name and DOB Missing	0			1 (<0.1%)		
Re-register	0			1 (<0.1%)		
Closed System Pharmacies						
Reason(s) for Rejection[d]						
Zip Code Missing	N/A	0		N/A	33 (57.9%)	
PPAF Incomplete	N/A	5 (50.0%)		N/A	10 (17.5%)	
Prescriber ID not registered	N/A	0		N/A	9 (15.8%)	
PPAF terminated	N/A	5 (50.0%)		N/A	6 (10.5%)	
Prescriber last name did not match registered	N/A	0		N/A	6 (10.5%)	
PPAF Expired	N/A	3 (30.0%)		N/A	3 (5.3%)	

[a] Prescription successfully adjudicated for safety (i.e., successful REMS edit).and authorized for dispensing by insurance or cash bin (bin number).

[b] Percentages are based on the total number (N) of number of unique prescriptions that encountered at least one initial REMS-related rejection prior to being authorized for dispensing for the reporting period.

[c] Includes authorizations from pharmacies that transitioned into the TIRF REMS Access Program from other individual REMS programs.

[d] Prescriptions can be rejected for more than one reason.

For all pharmacies, the mean time to authorization for a prescription that experienced at least one initial REMS-related rejection was 4.9 days (Table 16). For closed system pharmacies it took a mean of 10 days compared with chain pharmacy stores and independent outpatient pharmacies that took a mean of 5.1 days and 4.8 days, respectively. The increase in the mean time to authorization between all pharmacies and closed system pharmacies was primarily due to one closed system pharmacy outlier which took 61 days to fill from the original reject date. The claim had been rejected for a patient not having a completed PPAF on file.

Table 16 Time to Authorization for a Prescription that Experienced at Least One Initial REMS-Related Rejection

	Current Reporting Period 29OCT2013 to 28OCT2014	Cumulative 28DEC2011 to 28OCT2014
Total Mean Time For Prescription to be Authorized[a] (Days)[b]	4.903	3.327
Inpatient Pharmacies	--	--
Chain Pharmacy Stores	5.098	4.027
Independent Outpatient Pharmacies	4.820	3.048
Closed System Pharmacies	10.044	6.291
Total Median Time For Prescription to be Authorized[a] (Days)	1.055	0.157
Inpatient Pharmacies	--	--
Chain Pharmacy Stores	1.727	0.998
Independent Outpatient Pharmacies	0.984	0.063
Closed System Pharmacies	2.475	1.124

[a] Prescriptions included were resolved in the current reporting period. Prescriptions may have been initially rejected in a previous reporting period.

[b] Time to authorization for a prescription that experienced at least one initial REMS-related rejection excludes prescriptions processed through the inpatient pharmacy process.

As described in Section 5.1.3., a total of 239 closed system pharmacy locations are currently enrolled in the TIRF REMS Access Program. These 239 pharmacy locations are represented by 7 closed system entities enrolled in the TIRF REMS Access Program. These entities include:

(b) (4)

- National Institutes of Health Clinical Center Pharmacy
- U.S. Department of Veterans Affairs
- (b) (4)

- DLA Troop Support
- (b) (4)

During the current reporting period, a total of 730 prescription authorizations were provided through these closed system pharmacy locations and 2,075 were authorized over the cumulative period (Table 17).

Table 17 Number of Prescription Authorizations per Closed System Pharmacy

	Current Reporting Period 29OCT2013 to 28OCT2014	Cumulative 28DEC2011 to 28OCT2014
Total Number of Closed System Pharmacy Prescription Authorizations	730	2,075

(b) (4)

(b) (4)

	Current Reporting Period 29OCT?	Cumulative
(b) (4)		(b) (4)

5.1.6 Barriers or Delays in Patient Access [Metric 14 and 15]

Prescriptions Dispensed Within First 10 Days after Patient Enrollment

Across all pharmacies, a total of 9,980 prescriptions were dispensed to 7,983 patients within the first 10 days after patient enrollment (Table 18). The majority of patients (7,956) were dispensed prescriptions by non-closed system pharmacies (9,946 prescriptions). Of the 3,289 patients who received prescriptions without a PPAF, the majority of patients (86.9%) received only 1 fill without a PPAF. A total of 4 patients received more than 3 prescriptions within 10 days without a PPAF on file. All 4 patients had their prescriptions filled through non-closed system pharmacies. It was observed that 4 patients potentially received more than 3 fills within the 10 day period without a PPAF on file. The data indicates these are isolated incidents that happened over 3 days and at 2 separate independent outpatient pharmacies. Both pharmacies have been contacted and the pharmacists verbally confirmed that each patient did not receive greater than 3 prescriptions in the 10 day period. One of the four patients now has a PPAF on file. The TIRF REMS Access Call Center continues to make outbound calls in an attempt to

obtain PPAFs for the 3 remaining patients. The root cause of this report will continue to be investigated and the outcome of this research will be reported in the 48-month assessment report.

Table 18 Prescriptions Dispensed During the First 10 Days after Passive Patient Enrollment

	Current Reporting Period 29OCT2013 to 28OCT2014				Cumulative[a,b] 28DEC2011 to 28OCT2014			
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Combined Pharmacies[d] N (%)**	**Total Pharmacies N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Combined Pharmacies[d] N (%)**	**Total Pharmacies N (%)**
Number of prescriptions dispensed during the first 10 days after patient enrollment	9,946	31	3	9,980	29,355	200	11	29,566
Number of patients dispensed a prescription during the first 10 days after enrollment	7,956	26	1	7,983	24,580	164	5	24,749
With PPAF[b]								
1 Fill	3,832 (48.2%)	5 (19.2%)	0	3,837 (48.1%)	9,660 (39.3%)	48 (29.3%)	1 (20.0%)	9,709 (39.2%)
2 Fills	902 (11.3%)	1 (3.8%)	0	903 (11.3%)	1,830 (7.4%)	8 (4.9%)	0	1,838 (7.4%)
3 Fills	136 (1.7%)	0	0	136 (1.7%)	268 (1.1%)	1 (0.6%)	0	269 (1.1%)
>3 Fills	22 (0.3%)	0	0	22 (0.3%)	61 (0.2%)	2 (1.2%)	0	63 (0.3%)
Without PPAF[b,c]								
1 Fill	2,843 (35.7%)	17 (65.4%)	0	2,860 (35.8%)	11,969 (48.7%)	96 (58.5%)	1 (20.0%)	12,066 (48.8%)
2 Fills	323 (4.1%)	2 (7.7%)	0	325 (4.1%)	1,144 (4.7%)	5 (3.0%)	3 (60.0%)	1,152 (4.7%)
3 Fills	98 (1.2%)	1 (3.8%)	1 (100.0%)	100 (1.3%)	215 (0.9%)	4 (2.4%)	1 (20.0%)	220 (0.9%)
>3 Fills	4 (0.1%)	0	0	4 (0.1%)	9 (<0.1%)	0	0	9 (<0.1%)

[a] Cumulative data from the end of prior period may differ from the last period's report due to reconciliation of duplicate stakeholders.

[b] Percentages are based on the total number of patients for the period. Sum of percentages may be greater than 100 due to patients receiving prescriptions with and without a PPAF during the grace period.

[c] A patient may receive up to 3 fills in the first 10 days after enrollment without a PPAF.

[d] Patients who have filled a prescription at both a closed system pharmacy and a non-closed system pharmacy.

Prescriptions Dispensed Beyond 10 Days after Patient Enrollment

The TIRF REMS Access Program requires that each patient have a Patient-Prescriber Agreement Form (PPAF) submitted to the TIRF REMS Access Program by their prescriber within 10 days of their passive enrollment in order to continue to receive a TIRF medicine. Table 19 below shows the number of prescriptions dispensed beyond the first 10 days without a PPAF on file. From the inception of the TIRF REMS through the current reporting period, 751 prescriptions have been dispensed beyond the first 10 days without a PPAF; 6 prescriptions were in the current reporting period. These 6 prescription fills were all associated with the same patient. Patient records are created by the processing of a patient's first paid TIRF prescription (i.e., passive patient enrollment), or by the receipt of a PPAF. As a result of the passive patient enrollment process, the TIRF REMS Access Program has two systematic methods utilized to handle patient duplicates. First, the TIRF REMS Access Program systemically identifies and rectifies duplicate records utilizing patient matching logic consisting of key patient identifiers (i.e., Date of Birth, First Name, Last Name, and Zip Code). This occurs as part of the normal course of business when passive patient enrollments and PPAFs are processed; therefore duplicate patient records are not created. Second, the TIRF REMS Access Program systematically identifies potential patient duplicates, which generates a daily report to the TIRF REMS Access Program Call Center to ultimately determine if the record is a valid duplicate. Valid duplicates identified by the TIRF REMS Access Program Call Center are merged into one patient record. The data for the single patient receiving 6 prescriptions were merged into a single patient record upon confirmation of the correct birth date from the pharmacist.

Table 19 Prescriptions Dispensed Beyond the First 10 Days after Passive Patient Enrollment Without a PPAF

	Current Reporting Period 29OCT2013 to 28OCT2014				Cumulative[a,b] 28DEC2011 to 28OCT2014			
Parameter	**Filled at Non-Closed System Pharmacies N (%)**	**Filled at Closed System Pharmacies N (%)**	**Filled at Combined Pharmacies[b] N (%)**	**Filled at All Pharmacies N (%)**	**Filled at Non-Closed System Pharmacies N (%)**	**Filled at Closed System Pharmacies N (%)**	**Filled at Combined Pharmacies[b] N (%)**	**Filled at All Pharmacies N (%)**
Fills beyond the first 10 days Without PPAF	6	0	0	6	716	32	3	751

[a] Cumulative data from the end of prior period may differ from the last period's report due to reconciliation of duplicate stakeholders.

[b] A patient who has filled a prescription at both a closed system pharmacy and a non-closed system pharmacy.

5.2 Program Infrastructure and Performance [Metrics 16, 17, 18, 19]

5.2.1 Backup System for Prescription Validation [Metric 16]

During this reporting period there were no instances in which a backup system was used to validate a prescription due to pharmacy level problems, switch problems, or REMS database problems.

5.2.2 System Interruptions/Errors and Corrective Actions [Metric 17, 19]

A brief summary of issues identified as system errors and their corrective actions is presented below. Additional system errors that met the definition of non-compliance are presented in Section 6.

System Error #4: REMS Website Unavailable

Description

On 28 October 2013 at 6:48 a.m., the TIRF REMS Access Program was notified by a stakeholder that the REMS website was not available due to the homepage being inaccessible. Upon identification of the issue the website and database logs were immediately reviewed. It was determined that an external user took the home page temporarily offline and that the incident was isolated to the public-facing REMS website; no exposure or unauthorized access to the application or database occurred.

Root Cause

Intrusion of the public facing REMS website by an external user

Correction

The REMS website was restored to its original state on 28 October 2013 at 7:53 a.m. and additional scans of the REMS website were conducted to identify and fix any further vulnerability.

Resolution

Implementation of an annual REMS website scan (or after any major system functionality or software upgrade release) to identify any intrusion activity and adjustment of the website monitoring to alert the program to any identified intrusion activity.

System Error #5: TIRF re-enrollment records not merging with main record

Description

On 06 March 2014, the TIRF REMS Access Program identified an independent outpatient pharmacy that was inadvertently deactivated after re-enrollment due to a merging issue between enrollment and re-enrollment records. When a re-enrollment is initiated, a temporary re-enrollment record for that stakeholder is created within the application in order to track whether all required tasks are completed for the re-enrollment. Once all tasks associated with re-enrollment are completed, the temporary re-enrollment record merges into the main record and updates any data that were entered during re-enrollment.

The independent outpatient pharmacy had re-enrolled 6 days before their enrollment was expired; however, the temporary re-enrollment record did not successfully merge with the pharmacy's main enrollment record causing the pharmacy's enrollment to expire.

After further investigation it was found that an unexpected error had occurred due to the timing of the re-enrollment correspondence confirmation with the re-enrollment process. Due to a delay in sending the re-enrollment correspondence confirmation, the re-enrollment record merging process did not complete.

Root Cause

System coding error

Correction

The independent outpatient pharmacy was re-activated on 14 March 2014 and on 12 June 2014 the TIRF REMS Access Program confirmed that no claims were impacted.

Resolution

Implementation of a process to monitor system logs to immediately identify any similar occurrences and an update to system coding to prevent the overlap of the record merge process and the timing of the re-enrollment correspondence confirmation process were both completed on 06 June 2014.

System Error #6: Knowledge Assessment Failure Correspondence Displaying Incorrect Text for Question 11

Description

On 04 March 2014, the TIRF REMS Access Program identified that the correspondence being sent to stakeholders who fail the Knowledge Assessment included the incorrect question and answer options for question 11. The question/answer had been updated in a TIRF production release on 28 February 2014 in support of Modification 2. The Incomplete Knowledge Assessment correspondence was not updated to align with the revised question/answer.

Root Cause

Insufficient testing of correspondence related to the Knowledge Assessment when update(s) to questions/answers occurred

Correction

The Incomplete Knowledge Assessment correspondence was updated to display the correct question and answer for question #11 on 05 March 2014. A total of 28 stakeholders were impacted and all were contacted. A total of 27 of the 28 stakeholders successfully completed re-enrollment.

Resolution

Re-training on the process to test Knowledge Assessment correspondence when any changes are made to questions/answers.

System Error # 8: Direct Connection to Payers

Description

On 05 April 2012, the TIRF REMS Access Program identified three pharmacy switch vendors that had a direct connection to payers which meant that claims from certain pharmacies could be processed and paid without processing through the REMS edits. Three pharmacy switch vendors were affected.

Root Cause

Inadequate communication to switch vendors to eliminate direct connections to payers

Correction

As of 12 July 2012, all switch vendors identified as having direct connection to payers agreed to remove all direct connections to ensure claims are processed through the REMS edits.

Resolution

The REMS Vendor Communication Instruction and related correspondence for switch vendors was updated to include the following statement (or similar statement):

> "The switch vendors will ensure that their vendors and data aggregators do not send REMS transactions directly to payers; all REMS transactions are to be sent through the appropriate switch to ensure that all transactions are processed through the REMS Program."

The REMS Vendor Communication Instruction was published on 22 July 2014.

System Error # 21: Network Incident Impacting TIRF REMS

Description

On 22 July 2013, the TIRF REMS Access Program identified a network incident that impacted the REMS database. Two network connectivity losses caused 72 timeouts in REMS transactions which resulted in REMS rejections being received at the pharmacy.

Additionally, some stakeholder REMS records failed to import into the REMS database.

Root Cause

Insufficient internal processes for network change management requests

Correction

An investigation into the 72 timeouts was immediately performed. It was found that through the 72 timeouts, 17 claims were impacted. For each of these claims the pharmacy received a REMS rejection. The pharmacies were notified of the problem and claims were re-submitted. The final status of these claims included:

- 3 claims were reversed
- 5 claims were rejected based on REMS edits

- 9 claims were paid

The stakeholder records that failed to import into the REMS database were resubmitted and imported successfully.

Resolution

The network guidelines were updated to prevent this occurrence in the future. A network alert was installed to ensure timely identification of any similar issues. Additionally a process was established for internal communication after implementation of any network change to include the estimated timeline for changes.

System Error #25: TIRF REMS Transaction Bypassed REMS Edit

Description

On 22 July 2014, the TIRF REMS Access Program identified a transaction that came from a pharmacy switch vendor on 21 July 2014 and included a TIRF REMS National Drug Code (NDC) number but was not submitted to the REMS database for adjudication. The transaction routed directly to the third party insurance without passing through REMS edits. The switch vendor software had a coding error which caused the comparison to fail (i.e., the switch did not recognize it as a TIRF product).

Root Cause

No switch vendor audit to verify REMS compliance

Correction

On 27 July 2014 the transaction was reversed and successfully reprocessed. The pharmacy received REMS authorization as all stakeholders were enrolled in the REMS.

Resolution

The REMS Switch Vendor Communication Work Instruction was updated to include an email communication instructing switch vendors to conduct their own post-implementation audit of transactions to ensure adherence to the REMS program requirements.

5.2.3 REMS Call Center [Metric 18]

Table 22 below shows reasons for contacting the REMS Call Center by frequency (%). For presentation in the report, this table includes at least 80% of the total cumulative frequency. The most frequent reasons classified under the call reason were pharmacy: enrollment status inquiry (15.4%), PPAF status inquiry (13.8%), and pharmacy claim rejection (13.8%). The call reasons listed below in Table 22 represent 81.8% of calls to the Call Center for the current reporting period.

Table 20 Current Assessment Period Contact Reasons

Reason	Count	Percent[a]
Enrollment Status Inquiry	5,366	15.4%
PPAF Inquiry	4,816	13.8%

Reason	Count	Percent[a]
Pharmacy: Pharmacy Claim Rejection	4,801	13.8%
PPAF Follow Up	2,767	7.9%
Enrollment Follow Up	2,575	7.4%
Web Portal Logon Assistance	2,427	7.0%
Enrollment Form	1,696	4.9%
Other/Miscellaneous	1,557	4.5%
General Program Questions	1,525	4.4%
Website Inquiry	939	2.7%

[a] The total percentage presented in the table account for 81.8% of all reasons for contacting the Call Center.

There are no REMS related problems received by the REMS Call Center to report for the 36-month assessment report.

6 TIRF REMS ACCESS PROGRAM NON-COMPLIANCE

6.1 Audits

As part of non-compliance monitoring, TIRF REMS Access Program pharmacies may be subject to periodic data requests and/or audits. Such activities may occur for suspected non-compliance with program requirements based on program monitoring activities.

6.1.1 Closed System Pharmacy Audits [Metric 20]

The REMS Assessment Plan includes the following components for closed system pharmacy audits:

(1) Verification of training for all pharmacists dispensing TIRF products

(2) Numbers of prescription authorizations per closed system

(3) Reconciliation of data describing TIRF product prescriptions received by the closed system pharmacy with TIRF product dispensed to patients with a valid enrollment in the TIRF REMS Access Program.

The first component is accomplished through the enrollment process for closed system pharmacies. In order to become enrolled the authorized representatives must attest that all pharmacies dispensing TIRF products will be trained on the TIRF REMS Access Program requirements. The second component is done through the closed system pharmacy prescription authorization process. Closed system pharmacists are required to validate the enrollment status of the prescriber and patient prior to dispensing a TIRF product by calling or faxing the prescription details to the TIRF REMS Access Program. The TIRF REMS Access Program maintains records of prescription details and the associated REMS authorization. Table 19 provides information on all prescription authorizations by closed system pharmacy.

The third and final component includes reconciliation between the closed system pharmacy's dispensing data and the TIRF REMS Access Program's REMS authorizations. To conduct this reconciliation, the TIRF REMS Access Program requests dispensing records from the closed system pharmacies and compares the dispensing records to REMS authorization data from the TIRF REMS Access Program. After confirmation that the closed system pharmacy agrees to participate in the reconciliation, a formal written request for data was issued upon request to the authorized representative detailing the data to be provided and the deadline for submission. Specific data requested include:

- RX number for each prescription dispensed
- DEA number or NPI number of the facility that dispensed each prescription
- DEA number or NPI number of the prescriber that issued each prescription
- Date and time of each prescription transaction
- TIRF REMS Authorization code obtained for each prescription dispensed

Due to the structure of some closed system pharmacy networks, the headquarters may be unable to provide data for all pharmacy locations as no central data repository is in existence; each pharmacy location maintains their own data. In these cases a random sample of pharmacy locations was selected by the TIRF REMS Access Program for participation.

Findings from each investigation are reviewed with the NCRT and actions were taken in accordance with the Non-Compliance Protocol.

Of the 7 audits conducted during this reporting period, 5 closed system pharmacies were found to be non-compliant with the TIRF REMS Access Program requirements. Based on the identification of non-compliance, a non-compliance case was opened for each of these 5 closed system pharmacies. Below are the details of these investigations.

Closed System Pharmacy Non-Compliance Case 1: ID#167 (Case #13554751)

Request for Data

Based on an FDA inquiry on the reason for low utilization (based on REMS authorizations issued) and outreach that was initiated with the Department of Defense (DoD) in May 2013 to request dispensing records.

Investigation

Dispensing records were provided on 06 January 2014. The dispensing records contained data from program launch through September 2013 and included 282 instances where a TIRF product had been dispensed (both closed system and inpatient sites).

The dispensing records provided were compared to authorization data from the TIRF REMS Access Program and data discrepancies were found; however, due to the different identifiers used in both data sources, a full compare could not be completed.

The dispensing records provided were compared to authorization data from the TIRF REMS Access Program and data discrepancies were found; however, due to the different identifiers used in both data sources, a full compare could not be completed.

On 28 February 2014, a meeting was held with the DoD Corporate Headquarters' Authorized Representative to discuss the data discrepancies and next steps of the non-compliance investigation. The Authorized Representative stated that because of the transient nature of their pharmacy staff it is difficult to keep training current. The Authorized Representative agreed to assist in the investigation into the data discrepancies and agreed to provide additional dispensing records for NCRT review by 14 March 2014. The TIRF REMS Access Program also provided the DoD with closed system claim data for their research.

The DoD was unable to meet the 14 March 2014 deadline and the additional dispensing records were provided on 17 April 2014.

On 08 July 2014, an additional teleconference was held to discuss the data provided and next steps in the non-compliance investigation. The DoD Authorized Representative agreed to provide additional identifiers to the original dispensing data and exclude inpatient dispenses to attempt to tie the two data sources together. The deadline for the additional data was 08 August 2014. The requested dispensing records were provided on 31 July 2014.

Findings

On 31 July 2014, during a progress update teleconference, the DoD Authorized Representative confirmed that there were 330 instances where TIRF medicines were dispensed without a TIRF REMS authorization.

Outcome

On 13 August 2014, the NCRT requested that the DoD provide a written summary of the procedures established within the pharmacy locations to ensure on-going compliance, including:

- Obtaining signed closed system enrollment forms from all dispensing locations to ensure there is a point of contact within each site to hold accountable
- Meeting with the TIRF REMS Access non-compliance team monthly to reconcile data
- Re-education at sites provided by the authorized representative, as well as re-education provided by the TIRF REMS Access non-compliance team

A written summary was provided by the DoD Authorized Representative on 24 August 2014. A formal Notice for Non-Compliance was issued to the DoD on 09 September 2014.

As of the end of the reporting period, no additional non-compliance cases for the DoD have been identified.

Closed System Pharmacy Non-Compliance Case 2: ID#206 (Case #20099580)

Request for Data

On 21 February 2014, during outreach to (b) (4) to request feedback on the closed system pharmacy process for TIRF REMS Access Program, the Authorized Representative agreed to submit data associated with all instances where TIRF medicines were dispensed. A formal request for data correspondence was issued to (b) (4) on 08 April 2014, with a response requested by 08 May 2014.

Investigation

Dispensing records were received on 12 May 2014. The data represented their 5 enrolled pharmacies and included 499 instances where a TIRF product was dispensed via the closed system process. The dispensing records provided were compared to authorization data from the TIRF REMS Access Program.

Findings

A total of 42 instances were identified where a REMS authorization was not received prior to dispensing a TIRF product.

Outcome

A formal Notice for Non-Compliance, including a list of non-compliant events, was issued to the Authorized Representative.

As of the end of the reporting period, no additional non-compliance cases for (b) (4) have been identified.

Closed System Pharmacy Non-Compliance Case 3: ID#210 (Case #20312891)

Request for Data

On 27 February 2014, during outreach to the Veteran's Administration (VA) to request feedback on the closed system pharmacy process for TIRF REMS Access Program, the Authorized Representative agreed to submit data associated with all instances where TIRF medicines were dispensed. Since each VA site stores their own dispensing records (there is no central data storage), the Authorized Representative requested that the TIRF REMS Access Program select a sample of sites to provide dispensing records. A formal request for data correspondence was issued to the VA on 08 April 2014, with a response requested by 08 May 2014.

Investigation

Dispensing records were received on 12 May 2014. The data represented 3 pharmacy locations and included 43 instances where a TIRF product was dispensed via the closed system process. The dispensing records provided were compared to authorization data from the TIRF REMS Access Program.

Findings

A total of 43 instances were identified where a REMS authorization was not received prior to dispensing a TIRF product.

On 18 June 2014, the NCRT requested dispensing records for additional pharmacy locations. On 19 June 2014, the TIRF REMS Access Program provided a selection of 15 pharmacy locations (which represented 10% of the VA enrolled pharmacy locations) to provide dispensing records. The VA was asked to provide the requested data by 31 August 2014.

Dispensing records were received on 15 September 2014. Only two of the 15 pharmacy locations dispense TIRF medicines. The dispensing records provided were compared to authorization data from the TIRF REMS Access Program. Of the total 39 instances where drug was dispensed via the closed system process, 17 did not have REMS authorization prior to dispensing drug.

Outcome

A formal Notice for Non-Compliance was issued to the VA on 02 October 2014, with a request that the VA provide any preventative steps to be put in place to ensure ongoing compliance with their closed system dispensing locations.

Closed System Pharmacy Non-Compliance Case 4: ID 256 (Case # 21606341)

Request for Data

A formal request for data correspondence was issued to (b) (4) on 11 April 2014, with a response requested by 11 May 2014. On 13 May 2014, the Authorized Representative requested as extension to 20 June 2014 as the request needed to be reviewed by the legal and compliance department and patient information would need to be redacted from the data.

On 13 June 2014, the Authorized Representative advised that the request for data was approved by the legal and compliance department. An extension until 31 July 2014 was requested because the data would need to be pulled manually since the pharmacy was undergoing a transition to a new system.

On 28 July 2014 the Authorized Representative requested an additional extension to 02 September 2014 as a new automated system was being used by the pharmacy and compiling the data would take another month.

Investigation

Dispensing records were received on 17 September 2014. The data represented 2 pharmacy locations and included 205 instances where a TIRF product was dispensed via the closed system process. The dispensing records provided were compared to the authorization data from the TIRF REMS Access Program.

Findings

Of the total 205 instances where a TIRF product was dispensed, 76 instances were identified where a REMS authorization was not received prior to dispensing a TIRF product.

Outcome

On 30 September 2014, the TIRF REMS Access Program inquired whether (b) (4) still needed to dispense under the closed system process or if they now have the ability to enroll as

an independent outpatient pharmacy and process prescriptions electronically to communicate with the TIRF REMS Access system to obtain a REMS authorization prior to dispensing. The (b) (4) Authorized Representative advised that the pharmacy plans to enroll both locations as independent outpatient pharmacies as soon as a successful merge to the new automated system capable of electronic claims processing is complete. To ensure ongoing compliance for their pharmacy locations, the pharmacy plans to re-train all pharmacy staff within the next two months.

On 08 October 2014, a formal Notice for Non-Compliance was issued to the Authorized Representative.

As of the end of the reporting period, no additional non-compliance cases for (b) (4) have been identified.

Closed System Pharmacy Non-Compliance Case 5: ID 215 (Case # 20351073)

Request for Data

On 25 February 2014, during outreach to (b) (4) to request feedback on the closed system pharmacy process for TIRF REMS Access, the Authorized Representative agreed to participate in a data reconciliation to determine the pharmacy's compliance with the TIRF REMS Access Program. The Authorized Representative advised that (b) (4) does not have a central system or process that allows pulling of REMS authorization data from all individual locations. Each site would need to individually provide the data. The Authorized Representative proposed that the TIRF REMS Access Program provide REMS authorization data for randomly selected sites and provide the information to (b) (4) and (b) (4) would reconcile their own pharmacy's data to identify any non-compliance. This process has been used by (b) (4) to conduct audits for other REMS programs.

A formal request for data correspondence was issued to (b) (4) on 23 April 2014, with a response requested by 23 May 2014. On 20 May 2014, the Authorized Representative requested an extension to 30 June 2014 as (b) (4) was currently focused on re-enrollment for their closed system locations.

Investigation

Dispensing records were received on 03 June 2014. The data represented 3 pharmacy locations and included 148 instances where a TIRF product was dispensed via the closed system process. The dispensing records provided were compared to the authorization data from the TIRF REMS Access Program.

Findings

Of the total 148 instances where a TIRF product was dispensed, 5 instances were identified where a REMS authorization was not received prior to dispensing a TIRF product.

Outcome

On 03 July 2014, a formal Notice for Non-Compliance was issued to the Authorized Representative.

6.2 Inpatient Hospital Pharmacy Audits [Metric 21]

As per the TRIG's agreement with FDA as documented in an email on 22 September 2014, inpatient pharmacy hospital audits have not yet been conducted. The TRIG is developing a process to accomplish inpatient pharmacy audits. Therefore, inpatient pharmacy audit data will be included in the 48-month assessment report.

6.3 Stakeholder Non-Compliance [Metric 23, 24, 25, 26, 27, 28]

During the current reporting period, instances of potential stakeholder non-compliance with the TIRF REMS Access program were reviewed and investigated. A summary of the non-compliance activity is presented in Table 21.

Table 21 Non-Compliance Activity Reports by Stakeholder in the Current Reporting Period: 29 October 2013 to 28 October 2014

Stakeholder	Non-Compliance Activity	Non-Compliant Reason (categorized as reported by the stakeholder)	No. of events	No. of stakeholders
Non-Closed System Pharmacy	Submission of a claim that did not go through the REMS edits. A TIRF medicine was dispensed without verifying through the TIRF pharmacy management system that the prescriber is enrolled and active, and that the patient is enrolled or has not been inactivated in the program.	Not aware of requirement to process cash claims	6	No. w/1 report: 6
		Received reject but dispensed drug	3	No. w/1 report: 3
		Dispensed drug without obtaining an authorization	2	No. w/1 report: 2
		Not aware of cash claim *and* received reject but dispensed drug	1	No. w/1 report: 1
		No reason provided*	2	No. w/1 report: 2
	Inpatient Pharmacy dispenses for outpatient use	Dispensed drug without obtaining an authorization	1	No. w/1 report: 1
	Submission of inappropriately altered claim to meet TIRF REMS system requirements (e.g. changing prescriber)	Altered prescription details for a REMS authorization	1	No. w/1 report: 1
		No reason provided[a]	1	No. w/1 report: 1
Total Non-Closed System Pharmacy Cases			**17**	
Wholesaler/ Distributor	Wholesaler/Distributor fills an order for TIRF medicines for a non-enrolled stakeholder.	No reason provided[a]	1	No. w/1 report: 1
Total Wholesaler/Distributor Reports			**1**	
Prescriber	Prescriber failure to have a complete PPAF on file in a timely manner (5 or more patients enrolled by the prescriber without a complete PPAF on file, with each patient having greater than 10 working days lapse from initial enrollment date).	Not aware of PPAF requirement	25	No. w/1 report: 25
		Completed PPAF with patient but failed to send PPAF to TIRF REMS	19	No. w/1 report: 19
		Aware of PPAF requirements but failed to complete PPAF	15	No. w/1 report: 15
		No reason provided[a]	61	No. w/1 report: 53 No. w/2 report: 4

		Total Prescriber Reports	**120**	
Closed System Pharmacy	Dispensing prescriptions outside of the closed system authorization process.	Dispensed drug without obtaining an authorization	7	No. w/1 report: 7[b]
		Total Closed System Pharmacy Reports	**7**	
		Total Number of Reports During This Reporting Period	**145**	

[a] Stakeholder did not respond despite multiple outreach attempts.

[b] These 7 reports affected 5 closed system entities.

During the reporting period, there are 4 instances in which a pharmacy dispensed drug from a prescription written by a non-enrolled prescriber. The TIRF REMS Access Program reached out to the non-enrolled prescribers to assist with enrollment. Of those 4 instances, two of the prescribers ultimately completed enrollment and two communicated that they do not intend to enroll. In all 4 instances, the pharmacy that dispensed drug from a prescription written by a non-enrolled prescriber received re-education on program requirements and was issued a notice for non-compliance. No additional compliance cases for these pharmacies have been identified as of the end of the reporting period.

The TIRF REMS Access Program identified 4 unique non-enrolled DoD closed-system pharmacy locations that dispensed a TIRF product without REMS authorization in 16 instances. All 4 sites received drug from the same distributor. The distributor received re-education on program requirements and was issued a notice for non-compliance for distributing TIRF medicines to a non-enrolled pharmacy. In addition, the DoD was re-educated on the closed system pharmacy process to validate the prescription with the TIRF REMS Access Program and receive an authorization code prior to dispensing to patients.

There were no instances in which a TIRF was prescribed to an opioid non-tolerant individual reported during this reporting period. Additionally, there were no instances of inappropriate conversions between TIRF products reported during this reporting period.

The following tables (Table 22) list resolved NC cases and potential NC events that remained pending as of the end of the reporting interval.

Table 22 Non-Compliance Reports in the Current Reporting Period: 29 October 2013 to 28 October 2014

Report No.[1]	Report Description	Report Status	Mitigating Action
20	ID#121[1] (Case #15788194) **[24-Month Assessment Report Non-Compliance]** On 09 September 2013, a prescriber was contacted to request PPAFs for 5 patients who did not have one on file at least 10 days after enrollment. The prescriber provided PPAFs for 2 of the patients, but stated that 3 of the patients in question were not from his/her practice.	**Closed**	On 10 September 2013, the TIRF REMS Access Program contacted the independent pharmacy associated with the REMS authorized prescriptions for additional information. The pharmacy was unwilling to provide any information on these 3 patients and disconnected the call. All transactions from the pharmacy were reviewed by the NCRT. Seven claims involving 6 patients (including the 3 patients noted above) were identified where the patient's name was reversed (first name entered as last name, last name entered as first name) after the pharmacy received a rejection from the TIRF REMS Access Program for the reason "no PPAF on file." The pharmacist in charge was contacted on 04 October 2013 and the pharmacist in charge explained that these claims were from electronic prescriptions and processed with the information as it was provided (i.e., names were switched on original prescription). Based on this evidence, the pharmacy was issued a formal Warning for Non-Compliance letter. Additionally, the pharmacy was required to provide a CAP that was approved by the NCRT on 06 November 2013 stating that all pharmacy staff members have been trained on the program and have been educated on the importance of inputting correct patient data prior to transmitting pharmacy claims. Additionally all TIRF REMS claims will be checked and verified by a pharmacist. **[36-Month Assessment Report Update]** The NCRT monitored this pharmacy from 06 November 2013 to 03 February 2014 to ensure that REMS requirements were followed by the pharmacy and that no claims were altered. As of 03 February 2014 the pharmacy submitted all claims in accordance with program requirements and there were no claims found with suspected non-compliance. This non-compliance case was closed

Report No.[1]	Report Description	Report Status	Mitigating Action
			on 03 February 2014 after no further non-compliance cases were observed. Since closing the non-compliance case, no additional non-compliance cases for this pharmacy have been identified.
21	ID# 127[1] (Case# 12481943 & 15791475) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance on 12 March 2013 for not submitting PPAFs. On 17 September 2013, the prescriber was again identified for not submitting PPAFs for an additional 11 patients who were at least 10 days past enrollment. The TIRF REMS Access Program made 3 attempts to contact the prescriber, but was advised by the prescriber's office staff that the prescriber "refused to come to the phone regarding PPAF calls from TIRF REMS Access Program." By 21 October 2013, only 1 of the 11 outstanding PPAFs were received, and 3 additional patients were identified who did not have a PPAF on file at least 10 days after enrollment. The prescriber submitted none of the outstanding 13 PPAFs. Additionally, seven new patients had been enrolled without a PPAF on file outside of the 10-day window. Bringing the prescribers' total to 20 patients enrolled without a PPAF. A warning letter requesting a corrective action was issued to the prescriber 05 November 2013. **[36-Month Assessment Report Update]**	**Closed**	The TIRF REMS Access Program re-educated the prescriber on 03 October 2014. The prescriber advised that he thought his previous non-compliance cases were associated to his previous practice location. The prescriber was re-educated that non-compliance is associated with the prescriber directly, not the practice location. The prescriber stated that he now understands and will work with his office staff to ensure all PPAFs are submitted in the future. The prescriber submitted 4 of the 6 outstanding PPAFs. A second Warning Letter for non-compliance was submitted to the prescriber requiring that a CAP be submitted by 10 November 2014. The prescriber submitted the CAP the same day. The prescriber stated that he would make sure that each patient signs a form prior to leaving the office. The CAP was approved by the NCRT on 22 October 2014. Since closing this non-compliance case, no additional non-compliance cases for this prescriber have been identified.

Report No.[1]	Report Description	Report Status	Mitigating Action
	The prescriber failed to submit the corrective action by the deadline of 26 November 2013 and upon contacting the prescriber for a status update, the TIRF REMS Access Program was notified that the prescriber was no longer with the practice. The NCRT reviewed the case details and decided to proceed with suspending the stakeholder if a corrective action was not received by 09 January 2014. The prescriber's former office was verbally provided this tentative date for suspension so alternate arrangements could be made for any patients continuing therapy. On 13 December 2013, the prescriber was successfully contacted at his new office. He stated that he did not receive the Warning Letter prior to leaving his previous practice. The prescriber was re-educated on the TIRF REMS Access Program requirements and he advised that he would work to submit the corrective action by the deadline of 09 January 2014. The prescriber failed to submit the corrective action and was suspended on 09 January 2014. The prescriber was notified to submit a corrective action by 24 January 2014 in order to be reinstated in the TIRF REMS Access Program. A CAP was received on 14 January 2014 stating that the prescriber will ensure that PPAFs are submitted the same day as when the prescription is written or at		

Report No.[1]	Report Description	Report Status	Mitigating Action
	least within the 10 day grace period. To date, the prescriber has submitted PPAFs for 9 of the 20 initially identified patients. Since the prescriber has changed practices, he will be unable to submit PPAFs for the other 11 patients. The prescribers' suspension was removed on 15 January 2014. Since the suspension has been lifted, the prescriber has enrolled 5 new patients in the TIRF REMS Access Program. PPAFs were received in a timely manner for 3 of the patients. The PPAFs for the remaining 2 patients were received after the end of this reporting period. On 18 September 2014 the prescriber was again identified as not submitting PPAFs for 6 new patients.		
	ID#129[2] (Case # 12482115 & 16243002) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance on 8 March 2013 for not submitting PPAFs. **[36-Month Assessment Report Update]** On 21 October 2013, the prescriber was again identified as not submitting PPAFs for 5 new patients who were at least 10 days past enrollment.	**Closed**	The prescriber was contacted on 22 October 2013 and re-educated on the TIRF REMS Access Program requirements. The prescriber stated that he was aware of the TIRF REMS requirements and requested to be sent a list of patients who required PPAFs as he did not have time to discuss. After receiving the list of patients, the prescriber submitted 1 of the 5 PPAFs. On 05 November 2013, the prescriber was contacted by the TIRF REMS Access Program to discuss the outstanding PPAFs. The prescriber advised that he obtains a PPAF with each new patient for whom he prescribes a TIRF prescription and that there may be an issue with his administrative staff submitting the PPAFs. The prescriber stated he would investigate the PPAF submission process with his office staff and contact the Non-Compliance Team once the issue was identified and resolved. The prescriber contacted the TIRF REMS Access Program on 12 November

Report No.[1]	Report Description	Report Status	Mitigating Action
			2013 to inform the Non-Compliance Team that there was an issue with his office staff submitting the PPAFs in a timely manner. The prescriber submitted the remaining 4 outstanding PPAFs. On 22 November 2013 a second formal Notice for Non-Compliance was issued to the prescriber since this was a repeat offense of enrolling >5 patients without a PPAF by the prescriber. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
	ID#142[2] (Case# 12655619,16480983 & 18358046) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance on 26 February 2013 for not submitting PPAFs. **[36-Month Assessment Report Update]** On 06 November 2013, the pharmacy was again identified as not following the REMS requirements when a prescriber called to discuss a patient who was having difficulties obtaining their prescription. When the TIRF REMS Access Program advised the prescriber that the patients' PPAF had expired due to 180 days of no activity, the office staff stated that the patient was on monthly therapy. The pharmacy was contacted on 08 November 2013, and the authorized pharmacist confirmed that product was dispensed to the patient without REMS authorization in August, September, and October. All claims were cash claims. The pharmacy authorized designee was re-educated on the TIRF REMS Access Program		The TIRF REMS Access Program confirmed that based on claim data the pharmacy received a rejection when trying to process a prescription written by Dr. S on 28 February 2014. The authorized representative for the pharmacy was contacted on 05 March 2014 and advised that he had a prescription for that patient from an enrolled prescriber (Dr. I) not Dr. S. A copy of the prescription was requested. On 06 March 2014, Dr. I was contacted to understand his relationship with the patient. The prescriber stated that he wrote 1 prescription for the patient on (b) (6) upon discharge from the hospital. Dr. I stated that the pharmacy had contacted him requesting that he submit a prescription dated 06 February 2014 as the prescription received for the patient via fax from the prescriber's office was not legible. The prescriber advised the pharmacy that he had not written a prescription for the patient in February. Dr. I expressed his concern on this activity and indicated he would be submitting a detailed account of his interaction with the pharmacy in writing. When the prescriber contacted the patient, the patient's mother confirmed that the prescription that was written for the patient by Dr. I at discharge in January was mailed to the pharmacy not faxed. The TIRF REMS Access Program received a copy of the prescription from the

Report No.[1]	Report Description	Report Status	Mitigating Action
	requirements. On 15 November 2013, a second formal Notice for Non-Compliance letter was issued to the pharmacy. The pharmacy proactively provided a CAP on 22 November 2013 which stated that all pharmacy staff had received reinforcement training on the REMS requirement to receive a REMS authorization prior to dispensing TIRF medicines regardless of the method of payment. All re-trained staff was required to sign an acknowledgement that they understood the training. On 04 March 2014, a patient's mother called the TIRF REMS Access Program to report that the patient had been hospitalized. During this conversation, she stated that the patient's pharmacy contacted her on 28 February 2014 to notify her that the patients' doctor was not enrolled (Dr. S), but the pharmacy had dispensed drug for the patient.		pharmacy on 06 March 2014. The prescription was written by Dr. I and dated 06 February 2014. The TIRF REMS Access Program reviewed retrospective suspected non-compliance events for the pharmacy. Previous non-compliance cases had been open and investigated, but after no suspicious activity was detected the cases were closed. During investigation of these cases the pharmacy communicated that the issues were due to data error issues. On 10 March 2014, the TIRF REMS Access Program received a copy of the prescription from Dr. S that was written for the patient and dated 06 February 2014. A contact to Dr. I was attempted on 11 March 2014 to obtain the status of his detailed account of his interaction with the pharmacy in writing. The office staff communicated that Dr. I was out of the office on an emergency but he had drafted a letter that he plans to submit to the TIRF REMS Access Program. On 13 March 2014, the prescription written by Dr. I on (b) (6) upon the patient's discharge from the hospital was compared to the prescription received by the pharmacy that was dated 06 February 2014. The February prescription had void indications while the January prescription was presented clean. The pharmacy confirmed that the January prescription was received via FedEx which is why it was clean while the February prescription was provided via fax. As of 10 April 2014, the written account of the situation from either prescriber had not been received by the TIRF REMS Access Program. The pharmacy authorized representative was contacted and a formalized correspondence was sent to the pharmacy via fax on 10 April 2014 by the NCRT requesting additional information, CAP, and a written account of the incident be provided by 01 May 2014. On 25 April 2014, a written response and CAP was received from the pharmacy that detailed steps to eliminate manual errors made amongst the

Report No.[1]	Report Description	Report Status	Mitigating Action
			pharmacy staff. To prevent the issue in the future, the pharmacy stated they had added a dedicated pharmacist and licensed pharmacy technician to review and evaluate each TIRF REMS prescription that comes into the pharmacy and confirm the status of the patient, the certification of the doctor in the program and to make patients aware of proper protocol and procedure in regard to the TIRF REMS Access Program requirements. Additionally, a new pharmacy operating system would be installed to assist in accountability and tracing of all prescriptions. On 05 May 2014, the NCRT requested additional data from the pharmacy to ensure that the steps detailed in the CAP would address the non-compliance issues at the pharmacy. An addendum to the CAP was received from the pharmacy on 06 May 2014 which outlined the specific details for each instance where a data entry error occurred resulting in a non-compliance event. On 27 May 2014 the non-compliance case was closed and a Warning Letter was issued to the pharmacy acknowledging the receipt of the CAP and subsequent addendum. Since closing the non-compliance case, no additional non-compliance cases for this pharmacy have been identified.
	ID#147[2] (Case #12482016, 14089163, & 15934584) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a formal Notice of Non-Compliance on 09 April 2013 and a second formal Notice for Non-compliance on 27 August 2013 for not submitting PPAFs. **[36-Month Assessment Report Update]** On 29 September 2013, the prescriber was again identified for not submitting PPAFs for an additional	**Closed**	The TIRF REMS Access Program attempted to contact the prescriber 4 times from 30 September 2013 through 21 October 2013 for re-education on REMS requirements. The prescriber was unable to be reached. A list of patients missing PPAFs was provided via fax to the office staff at their request. The office staff additionally requested that all communication go through a specific office contact. On 07 November 2013, the TIRF REMS Access Program was notified that the prescriber was no longer affiliated with the practice. The office staff stated that no forwarding information for the prescriber was available. On 10 December 2013, additional outreach confirmed that the prescriber was

Report No.[1]	Report Description	Report Status	Mitigating Action
	5 patients who were at least 10 days past enrollment.		still affiliated with the practice. The office staff communicated that they had confused two prescribers in the practice, both of which are under investigation for non-compliance. The office staff stated that all communication needed to go through the specific office contact and requested that they receive no additional contact via phone for PPAFs; all PPAF requests must be provided via fax. The TIRF REMS Access Program re-faxed the list of patients with missing PPAFs to the prescriber's office. An additional 13 patients without a PPAF on file were identified, for a total of 18 patients without a PPAF on file. On 17 December 2013, a Warning Letter was sent to the prescriber requiring a Corrective Action Plan to be submitted by 07 January 2014. On 20 December 2013, a Corrective Action Plan was received stating that the prescriber was compliant with program requirements and all PPAFs are submitted online. Copies of the confirmations for online submissions of PPAFs were provided for 15 of the 18 total patients. All confirmations provided were from mid-December after initiation of the non-compliance outreach. An additional 15 patients were identified on 08 January 2014 as not having a PPAF on file at least 10 days past enrollment, for a total of 18 outstanding PPAFs. On 09 January 2014, the Corrective Action Plan was denied by the NCRT since the plan submitted as it did not specify what the prescriber would do to ensure ongoing compliance with REMS requirements. The prescriber's office was contacted and advised that the outstanding 18 PPAFs and a new Corrective Action Plan need to be submitted. A new version of the Corrective Action Plan was received on 10 January 2014, but it was signed by an office staff member. The TIRF REMS Access Program contacted the prescriber's office on 13 January 2014 to inform the office that the prescriber must sign the plan. A prescriber signed Corrective Action Plan was received on 14 January 2014, stating that PPAFs will be done the same day or within 10 days of a prescription being issued. All 18 outstanding PPAFs were submitted. The Corrective Action Plan was approved by the NCRT on 15 January 2014. Since closing the non-compliance case, no additional non-compliance cases

Report No.[1]	Report Description	Report Status	Mitigating Action
			for this prescriber have been identified.
	ID#152[2] (Case # 12482070 & 16449458) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a formal Notice for Non-Compliance letter on 12 June 2013 for not submitting PPAFs. **[36-Month Assessment Report Update]** On 05 November 2013, the prescriber was again identified as not submitting PPAFs for 5 new patients who were at least 10 days past enrollment.	**Closed**	The TIRF REMS Access Program attempted to contact the prescriber 4 times from 05 November 2013 to 15 November 2013 and was only able to speak with office staff. Staff advised that the person previously responsible for TIRF REMS Access Program requirements (non-HCP staff member) was no longer at the practice. A request for contact correspondence was issued to the prescriber on 19 November 2013. The prescriber failed to contact the TIRF REMS Access Program for re-education by the 10 December 2013 deadline. The prescriber submitted 4 of the 5 outstanding PPAFs between 05 November 2013 and 07 December 2013. The remaining PPAF was for a patient that was identified as not continuing therapy. On 20 December 2013, a second formal Notice for Non-Compliance letter was issued to the prescriber since this was a repeat offense of enrolling >5 patients without a PPAF by the prescriber. As of the end of the reporting period, the remaining 1 PPAF had not been submitted. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
	ID#162[2] (Case # 12481270 & 17070007) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a formal Notice for Non-Compliance letter on 08 April 2013. **[36-Month Assessment Report Update]** On 20 December 2013, the prescriber was again identified during routine compliance monitoring as not submitting PPAFs for an additional 5 patients who were at least 10 days past enrollment.	**Closed**	On 06 January 2014, the TIRF REMS Access Program attempted to contact the prescriber for re-education on the REMS requirements. The prescriber was unavailable for re-education. The office staff requested a list of patients with missing PPAFs and the list was faxed to the office by the TIRF REMS Access Program. On 14 January 2014, during an outbound call the office staff advised that all patients on the list of missing PPAFs were one-time only prescriptions and they were attempting to get these patients to come back into the office to complete PPAFs but to date had been unsuccessful. The TIRF REMS Access Program reiterated that the prescriber needed to be re-educated directly to which the office staff advised that the prescriber would not be available as the prescriber's Schedule II DEA license was suspended by the Texas Medical Board on 11 December 2013 and is currently under review and awaiting final outcome.

Report No.[1]	Report Description	Report Status	Mitigating Action
			On 15 January 2014, the prescriber was suspended in the TIRF REMS Access Program pending additional information from the Texas Medical Board regarding the status of the prescribers' DEA license. On 17 January 2014, verbal and written confirmation was received from the Texas Medical Board and the prescriber was deactivated in the TIRF REMS Access Program. A Notice of Deactivation was sent to the prescriber on 20 January 2014 notifying the prescriber that he had been deactivated in the program, and that he could re-enroll in the TIRF REMS Access Program upon reinstatement of his DEA license. The 5 outstanding PPAFs from this non-compliance offense were not received as these patients were not continuing therapy.
	ID#164[1] (Case # 12481214, 14089142, 16966461 & 19073509) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance letter on 07 March 2013 and a second Notice for Non-Compliance letter on 11 July 2013 for not submitting PPAFs. **[36-Month Assessment Report Update]** On 13 December 2013, the prescriber was identified as not submitting PPAFs for 11 new patients. The TIRF REMS Access Program attempted to contact the prescriber on 16 December 2013 for re-education on the REMS requirements. A message was left for the prescriber and the office staff was re-educated on the PPAF requirements. On 19 December 2013, the office staff requested a list of patients with missing PPAFs and the list was provided by the TIRF REMS Access Program via fax. On 23 December 2013, the TIRF REMS Access	**Closed**	The prescriber was contacted and re-educated on the REMS requirements on 17 April 2014. The prescriber advised that he was now on the pain board for a specific TIRF product and cannot be found non-compliant with program guidelines any longer. The TIRF REMS Access Program explained to the prescriber that the program is mandated by the FDA and no stakeholders are exempt from program requirements. The prescriber stated that the TIRF REMS Access Program should consider patient volume when assessing what is deemed as non-compliance. As of the 22 April 2014, the prescriber submitted 7 of the 9 PPAFs. On 24 April 2014, the NCRT approved suspension of the prescriber, pending successful outreach to the prescriber to inform him of the potential patient access issues. The prescriber was suspended and notified of the suspension on 29 April 2014. The prescriber submitted a Corrective Action Plan stating that the issue within the office was due to frequent turnover in staff and poor training for new staff. As a solution, the office will appoint someone in addition to the prescriber to oversee implementation of the TIRF REMS requirements. The prescriber also provided his personal cell phone number so that the TIRF REMS Access Program can contact him directly for any PPAF issues. The Corrective Action Plan was approved by the NCRT and prescriber's suspension was lifted on 30 April 2014. To ensure compliance with timely

Report No.[1]	Report Description	Report Status	Mitigating Action
	Program attempted to contact the prescriber for re-education on the REMS requirements. A message was left for the prescriber. An additional 6 patients were identified without a PPAF at least 10 days past enrollment on 30 December 2013 for a total of 17 patients without a PPAF at least 10 days past enrollment. The physician was again unavailable when contacted. The prescriber submitted 8 of the 17 outstanding PPAFs. As of 20 January 2014, the prescriber had not contacted the TIRF REMS Access Program for re-education. A Warning for Non-Compliance with a request for a Corrective Action Plan was issued to the prescriber on 24 January 2014. The deadline for the Corrective Action Plan was 14 February 2014. The prescriber submitted 5 of the 8 outstanding PPAFs. On 06 February 2014, an additional 16 patients were identified without a PPAF at least 10 days past enrollment. The TIRF REMS Access Program attempted to contact the prescriber on 07 February 2014. The office staff was re-educated on PPAF requirements and a message was left for the prescriber reminding him of the 14 February 2014 deadline for the Corrective Action Plan. The TIRF REMS Access Program attempted to contact the prescriber on 11 February 2014 and spoke with the prescribers PA. The prescriber's PA was re-educated on PPAF requirements, and advised of the deadline for the Corrective Action Plan and the need to speak to the prescriber regarding the 19 patients for whom PPAFs had not been submitted. The prescriber's PA requested that all documents be re-		PPAF submission the TIRF REMS Access Program conducted daily PPAF monitoring for the prescriber from 01 May 2014 through 27 June 2014. During this time no patients were identified as not having a PPAF on file at least 10 days past enrollment. The prescriber submitted all of the 9 outstanding PPAFs. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.

Report No.[1]	Report Description	Report Status	Mitigating Action
	faxed to the office so she could review them with the prescriber. All requested documents were faxed to the office and the prescriber contacted the program on 11 February 2014 and was re-educated. The prescriber was unable to explain why PPAFs had not been received for the 19 patients as he provides one for each patient via fax. The prescriber's Corrective Action Plan was received on 17 February 2014. On 18 February 2014, the prescriber submitted 14 of the 19 PPAFs and stated that he would work with his office staff to submit the remaining 5 PPAFs. The Corrective Action Plan was approved by the NCRT on 20 February 2014. All 5 outstanding PPAFs were submitted. On 03 April 2014, the prescriber was again identified as not submitting PPAFs for 9 new patients.		
	ID#165[1] (Case # 12481066, 14088956, 16966742 & 19221013) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance Letter on 14 March 2013 and a second formal Notice for Non-Compliance on 12 August 2013 for not submitting PPAFs. **[36-Month Assessment Report Update]** On 13 December 2013, the prescriber was identified as not submitting PPAFs for 10 new patients. The TIRF REMS Access Program attempted to contact the prescriber on 18 December 2013. A message was left for the prescriber and the office staff was re-educated on PPAF requirements. On 07 January 2014, a non-HCP from the prescriber's office		The TIRF REMS Access Program attempted to contact the prescriber multiple times between 10 April 2014 and 30 April 2014. A list of patients missing PPAFs was faxed to the prescriber's office as requested on 16 April 2014. On 18 April 2014, the TIRF REMS Access Program verified that all 6 PPAFs were submitted via the website, but after the non-compliance case had been initiated. Additional outreach attempts were made from 21 April 2014 to 30 April 2014 to re-educate the prescriber on TIRF REMS Access Program requirements. On 12 May 2014, the TIRF REMS Access Program became aware that the prescriber had been arraigned in federal court on 06 May 2014 on charges of healthcare fraud and distribution of controlled substances. The prescriber was released on a bond that states he cannot prescribe controlled substances. On 14 May 2014, the prescriber contacted the TIRF REMS Access Program with a request to opt out of the program. The request was submitted in writing on the prescriber's letterhead. The prescriber was deactivated in the program.

Report No.[1]	Report Description	Report Status	Mitigating Action
	contacted the program requesting a list of patients missing PPAFs. A list was faxed by the TIRF REMS Access Program to the office. On 08 January 2014 a request for contact correspondence was issued to the prescriber since there had been multiple unsuccessful attempts to reach the prescriber for re-education. The prescriber failed to contact the TIRF REMS Access Program for re-education by the 22 January 2014 deadline. A Warning for Non-Compliance with a request for a Corrective Action Plan was issued to the prescriber on 29 January 2014. The prescriber failed to submit a Corrective Action Plan by the deadline of 19 February 2014. The TIRF REMS Access Program contacted the prescriber on 20 February 2014, and the prescriber requested an extension to his deadline agreeing to submit a Corrective Action Plan by 25 February 2014. The Corrective Action Plan was received on 25 February 2014 and approved by the NCRT on 26 February 2014. All 10 outstanding PPAFs were submitted. On 10 April 2014, the prescriber was again identified as not submitting PPAFs for 6 new patients.		The prescriber has not contacted the program since 14 May 2014. The TIRF REMS Access Program will require NCRT approval if the prescriber attempts to enrolls in the program again.
	ID#166(Case #17402306) On 06 November 2013, (b) (4) was identified as dispensing a TIRF product for an outpatient without receiving REMS authorization. The pharmacy had initially been enrolled as an inpatient pharmacy, but also dispenses for outpatient use. The pharmacy attempted to enroll as an outpatient pharmacy but was unable to finalize their outpatient enrollment since they were unable to run		The TIRF REMS Access Program re-educated the pharmacy on the closed system authorization process and requirements on 08 November 2013. On 12 December 2013, the pharmacy confirmed that the product had been ordered under the inpatient pharmacy enrollment. Dispensing records for all TIRF medicines dispensed through (b) (4) were requested by the TIRF REMS Access Program. On 17 January 2014, the requested dispensing records were received. The TIRF REMS Access Program compared the dispensing records to the REMS

Report No.[1]	Report Description	Report Status	Mitigating Action
	test transactions. To accommodate a patient who was currently waiting for a TIRF medication, the pharmacy had enrolled on 05 September 2013 as a closed system pharmacy, but the TIRF medication was dispensed on 03 September 2013, prior to this enrollment date.		authorization data. The TIRF REMS Access Program confirmed that the only instance of non-compliance occurred on 03 September 2014 when the pharmacy dispensed for outpatient use prior to their closed system enrollment. On 07 February 2014, a formal Notice for Non-compliance was issued to the pharmacy. Since closing the non-compliance case, no additional non-compliance cases for this pharmacy have been identified.
	ID#169[2] (Case #12481169 & 17657140) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a formal Notice for Non-Compliance letter on 31 March 2013 for not submitting PPAFs. **[36-Month Assessment Report Update]** On 03 February 2014, the prescriber was again identified as not submitting PPAFs for 9 new patients since re-education on 31 March 2013.	**Closed**	On 12 February 2014, the prescriber was contacted and re-educated on the TIRF REMS Access Program requirements. The prescriber stated that he does complete a PPAF for each new patient and that there may be an issue with his office staff as there has been turnover since the last non-compliance investigation. The prescriber advised that he takes the program very seriously and will address the matter with his staff. On 17 February 2014, the prescriber's office called to request a list of patients that were missing PPAFs. The list was faxed to the office. The prescriber submitted all 9 outstanding PPAFs. On 24 February 2014 a second formal Notice for Non-Compliance was issued to the prescriber since this was a repeat offense of enrolling >5 patients without a PPAF by the prescriber. The prescriber submitted 0 of the remaining 4 PPAFs had not been submitted. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
	ID#177[2] (Case #13861166 & 18732022) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a formal Notice for Non-Compliance on 13 August 2013 for not submitting PPAFs. **[36-Month Assessment Report Update]**	**Closed**	The TIRF REMS Access Program attempted to contact the prescriber on 20 March 2014 and spoke with the office staff. A list of patients missing PPAFs was provided verbally. A message was left for the prescriber to contact the TIRF REMS Access Program for re-education. On 07 April 2014, a request for contact correspondence was sent to the prescriber after multiple unsuccessful outreach attempts between 25 March 2014 and 07 April 2014. On 07 April 2014, the prescriber contacted the TIRF REMS Access program

Report No.[1]	Report Description	Report Status	Mitigating Action
	On 20 March 2014, the prescriber was identified as not submitting PPAFs for 6 new patients since re-education occurred on 13 August 2013.		and was re-educated on the program requirements. He advised that he assumed his office staff was submitting the PPAFs. On 09 April 2014, a second formal Notice for Non-Compliance was issued to the prescriber since this was a repeat offense of enrolling >5 patients without a PPAF by the prescriber. The prescriber submitted all 6 outstanding PPAFs. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
	ID#179[2] (Case #12482456, 18919365 & 20277540) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance on 18 March 2013 for not submitting PPAFs. **[36-Month Assessment Report Update]** On 27 March 2014 the prescriber was identified as not submitting PPAFs for 16 patients. The TIRF REMS Access Program attempted to contact the prescriber on 02 April 2014 and spoke with the office staff. A list of patients missing PPAFs was faxed to the office per their request. A message was left for the prescriber during this contact and again on 04 April 2014. The prescriber submitted all 16 PPAFs. On 11 April 2014 a second formal Notice for Non-Compliance was issued to the prescriber since this was a repeat offense of enrolling >5 patients without a PPAF by the prescriber. On 16 June 2014 the prescriber was again identified as not submitting PPAFs for 6 new patients who were at least 10 days past enrollment. The TIRF REMS Access Program attempted to	**Closed**	The TIRF REMS Access Program re-educated the prescriber on 10 November 2014. The prescriber stated that he has been completing PPAFs and he is not sure why his office staff has not been submitting them. The prescriber submitted none of the 6 outstanding PPAFs. A second Warning for Non-Compliance was issued to the prescriber 13 November 2014 requiring that the prescriber submit a CAP by 04 December 2014. The prescriber submitted a CAP on 01 December 2014 stating that he has met with all of his current staff members to ensure that they understand the importance of the TIRF REMS Program and thoroughly understand the protocol for the completion and submission of PPAFs. Additionally, the prescriber has made several changes within his office, including having TIRF REMS forms readily available to be signed in every patient room and personally reviewing his schedule daily to confirm that every patient who was prescribed a TIRF medicine has been REMS enrolled. The CAP was approved by the NCRT on 03 December 2014 and this non-compliance case was closed. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.

Report No.[1]	Report Description	Report Status	Mitigating Action
	contact the prescriber multiple times between 18 June 2014 and 27 June 2014. On 30 June 2014 a request for contact correspondence was issued to the prescriber as all outreach attempts had been unsuccessful. The prescriber was re-educated on the TIRF REMS Access Program requirements during an inbound call on 01 July 2014. The prescriber stated that he does complete PPAFs with each patient and relies on his office staff at multiple locations to submit the PPAFs to the program. The prescriber advised that he understands that it is his responsibility to submit a PPAF for each new patient prior to their first prescription. The prescriber submitted 5 of the 6 outstanding PPAFs. The last outstanding PPAF will not be submitted as it was for a patient identified as not continuing therapy. On 11 July 2014 the prescriber was issued a Warning with a request for a Corrective Action Plan. A Corrective Action Plan was received on 14 July 2014 and was denied by the NCRT as it did not align with the re-education that it was the prescriber's responsibility to submit PPAFs for each patient. The prescriber was advised that a revised Corrective Action Plan was required. On 24 July 2014 a revised Corrective Action Plan was provided by the prescriber stating that moving forward the prescriber would have a folder in each exam room and he would ensure the patient signs while he was with them. The prescriber also stated that he would take personal responsibility to make sure patients are educated and PPAFs are signed. The Corrective Action Plan was approved by the NCRT		

Report No.[1]	Report Description	Report Status	Mitigating Action
	and this non-compliance case was closed. On 10 November 2014 the prescriber was again identified as not submitting PPAFs for 6 new patients.		
	ID#180 (Case #17656072, 19221002 & 19890126) On 31 January 2014 the prescriber was identified as not submitting PPAFs for 6 patients. On 03 February 2014, the prescriber's office staff was re-educated on PPAF requirements. A list of patients missing PPAFs was faxed to the office at the request of the office staff. A request for contact correspondence was issued to the prescriber after multiple unsuccessful outreach attempts between 06 February 2014 and 14 February 2014. The prescriber failed to contact the TIRF REMS Access Program for re-education by the deadline of 10 March 2014. On 12 March 2014, a formal Notice for Non-Compliance was issued to the prescriber. All of the 6 PPAFs were submitted. On 10 April 2014, the prescriber was again identified as not submitting PPAFs for 10 patients. The TIRF REMS Access Program contacted the prescriber on 10 April 2014 and provided re-education on the requirements of the program. The prescriber advised that he was not aware that his office staff was not completing the PPAFs and that he was not aware that a Notice of Non-Compliance was issued previously as he was out of the country at the time. The prescriber acknowledged that he understood it was his responsibility to complete and sign a PPAF with each new patient before writing the patient's first	**Closed**	The TIRF REMS Access Program attempted to contact the prescriber on 05 June 2014. The office staff advised that none of the 5 patients were the prescriber's patients. Copies of all 5 prescriptions were obtained from the pharmacy on 12 June 2014. All prescriptions were written by the prescriber. The prescriber was contacted on 19 June 2014 and re-educated on the TIRF REMS Access Program requirements. He confirmed that the patients were his patients and stated that he was not aware that it was his responsibility to submit PPAFs. The prescriber submitted all 5 PPAFs. On 11 July 2014 the prescriber was issued a Warning letter requiring a Corrective Action Plan be submitted. On 31 July 2014 a Corrective Action Plan (version 1) was received. The NCRT denied the plan as it did not address how the prescriber would complete PPAFs for outpatient dispensing in a hospital setting. The prescriber was advised that a revised Corrective Action Plan was required. On 11 August 2014 a revised Corrective Action Plan (version 2) was received. The plan again did not address what was requested after the denial of the first version of the Corrective Action Plan. The TIRF REMS Access Program attempted to contact the prescriber multiple times to discuss that a revised Corrective Action Plan was required. On 22 August 2014 a revised Corrective Action Plan (version 3) was received before the TIRF REMS Access Program could successfully contact the prescriber to discuss. The NCRT again denied the plan. A written request for a revised Corrective Action Plan was submitted to the prescriber on 29 August 2014. On 23 September 2014, an updated Corrective Action Plan (version 4) was received by the TIRF REMS Access Program. This revised plan was reviewed

Report No.[1]	Report Description	Report Status	Mitigating Action
	prescription for a TIRF medicine. None of the outstanding 10 PPAFs were submitted and an additional patient without a PPAF on file was identified, making a total of 11 outstanding PPAFs. The prescriber submitted 8 of the 11 PPAFs. The other 3 outstanding PPAFs would not be submitted as the patient was identified as not continuing therapy. On 18 April 2014 a second formal Notice for Non-Compliance was issued to the prescriber since this was a repeat offense of enrolling >5 patients without a PPAF by the prescriber. On 19 May 2014, the prescriber was identified as not submitting PPAFs for 5 new patients who were at least 10 days past enrollment.		and approved by the NCRT on 24 September 2014. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
	ID#187[2] (Case #15425572 & 18641073) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance on 24 September 2013 for not submitting PPAFs. **[36-Month Assessment Report Update]** On 17 March 2014, the prescriber was identified for not submitting PPAFs for 9 new patients who were at least 10 days past enrollment. The TIRF REMS Access Program attempted to contact the prescriber on 19 March 2014. The office staff was re-educated and a list of patients missing PPAFs was faxed to the office. A message was left for the prescriber. On 15 April 2014 a request for contact correspondence was sent to the prescriber after multiple unsuccessful contact attempts between 26	**Closed**	The TIRF REMS Access Program re-educated the prescriber on 10 November 2014. The prescriber stated that he has been completing the PPAFs and is not sure why his office staff has not been submitting them, but he is going to investigate the issue immediately. The prescriber submitted none of the 9 outstanding PPAFs. The prescriber was issued a second Warning for Non-Compliance on 13 November 2014 requiring that a CAP be submitted by 04 December 2014. The prescriber submitted a CAP on 18 November 2014 stating that the office had technical issues with the website causing PPAFs to not be submitted in a timely manner. The prescriber advised that moving forward they will submit PPAFs via fax and keep paper files to ensure tracking of completion of enrollment. The prescriber submitted 8 of the 9 outstanding PPAFs. The prescriber is unable to submit the last outstanding PPAF as the patient was identified as not continuing therapy. On 20 November 2014, the TIRF REMS Access Program contacted the prescriber to get clarification on what difficulties the prescriber had accessing the website. An addendum to the CAP was received on 21 November 2014 clarifying that the website had worked fine initially but then they started

Report No.[1]	Report Description	Report Status	Mitigating Action
	March 2014 and 14 April 2014. The prescriber failed to contact the team for re-education by the deadline of 06 May 2014. A call from the prescriber's office staff regarding PPAF requirement questions was received on 09 May 2014. The TIRF REMS Access Program re-educated the office staff and the prescriber during the call. The prescriber stated that he now understood that it is his responsibility to ensure that each new patient has a PPAF on file. The prescriber submitted 7 of the 9 outstanding PPAFs. The other 2 outstanding PPAFs would not be submitted as the patients were identified as not continuing therapy. A second formal Notice for Non-Compliance was issued to the prescriber on 19 May 2014 since this was a repeat offense of enrolling >5 patients without a PPAF by the prescriber. On 06 November 2014 the prescriber was again identified as not submitting PPAFs for 9 new patients.		having technical issues with the website. The CAP and addendum were approved by the NCRT on 03 December 2014 and this non-compliance case was closed. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
	ID#188[2] (Case #13861174 & 18918829) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance on 20 September 2013 for not submitting PPAFs. **[36-Month Assessment Report Update]** On 27 March 2014 the prescriber was identified as not submitting PPAFs for 6 new patients who were at least 10 days past enrollment. The TIRF REMS Access Program attempted to contact the prescriber multiple times between 31	**Closed**	The TIRF REMS Access Program re-educated the prescriber on 18 November 2014. The prescriber stated that the reason he has not submitted PPAFs is due to user error in completing the attestation electronic signature on the TIRF REMS website. The prescriber was reminded that the office will receive a confirmation from the website when a PPAF is submitted correctly and also provided directions for how to successfully complete and submit the PPAF with the electronic signature. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.

Report No.[1]	Report Description	Report Status	Mitigating Action
	March 2014 and 24 April 2014. A request for contact correspondence was issued to the prescriber on 24 April 2014. On 20 April 2014, the prescriber's office staff contacted the TIRF REMS Access Program to obtain a list of patients missing PPAFs. The office staff was re-educated on the TIRF REMS Access Program requirements and was verbally provided a list of patients missing PPAFs. On 12 May 2014 the prescriber was re-educated on the TIRF REMS Access Program requirements during an outbound call. The prescriber stated that PPAFs are submitted via fax and was not aware that PPAFs could be submitted online. The prescriber was provided his login information and provided a tutorial on how to submit PPAFs online. The prescriber submitted 5 of the 6 outstanding PPAFs. The last outstanding PPAF would not be submitted as the patient was identified as not continuing therapy. On 20 May 2014 a second formal Notice for Non-Compliance was issued to the prescriber since this was a repeat offense of enrolling >5 patients without a PPAF by the prescriber. On 06 November 2014 the prescriber was again identified as not submitting PPAFs for 6 new patients.		
	ID#195[2] (Case #12925513 & 19073027) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance on 17 May 2013 for not submitting PPAFs.	**Closed**	The TIRF REMS Access Program attempted to contact the prescriber on 03 April 2013 for re-education. A message was left for the prescriber and the office staff was re-educated. A list of the patients missing PPAFs was requested and was faxed to the office. A request for contact correspondence was issued to the prescriber on 24 April 2014 after multiple unsuccessful contact attempts between 11 April 2014 and

Report No.[1]	Report Description	Report Status	Mitigating Action
	[36-Month Assessment Report Update] On 03 April 2014 the prescriber was identified as not submitting PPAFs for 8 new patients who were at least 10 days past enrollment.		24 April 2014. The prescriber failed to contact the TIRF REMS Access Program for re-education by the deadline of 15 May 2014. An additional 3 patients without PPAFs were identified for a total of 11 outstanding PPAFs. On 21 May 2014 a Warning Letter was issued to the prescriber, requiring that a Corrective Action Plan be submitted by 11 June 2014. A Corrective Action Plan was received on 11 June 2014. The Corrective Action Plan was denied by the NCRT as the plan did not address why the non-compliance event occurred. Additional unsuccessful contacts were made in an attempt to re-educate the prescriber and to request a revised Corrective Action Plan. The prescriber submitted 1 of the outstanding PPAFs and during an outreach attempt, the office staff communicated that the remaining 10 outstanding PPAFs would not be submitted, as the patients were not continuing therapy. A copy of the Corrective Action Plan template was faxed at the request of the office staff. On 26 June 2014, the NCRT decided to suspend the prescriber until a revised CAP was received. The TIRF REMS Access Program contacted the prescriber's office to communicate the suspension. The office staff stated that they would ensure a revised Corrective Action Plan is submitted immediately. A revised Corrective Action Plan was received on 27 June 2014. The NCRT required additional information before approval of the Corrective Action Plan. The prescriber submitted a supplement to the Corrective Action Plan and the plan was approved on 30 June 2014. The prescriber's suspension was removed and he was monitored until 01 August 2014. The non-compliance case was closed after no additional non-compliance cases were identified during this time period. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
	ID#204[2] (Case #12922697 & 19357451) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance on 14 June 2013 for not submitting	**Closed**	The TIRF REMS Access Program attempted to contact the prescriber multiple times between 21 April 2014 and 07 May 2014. A request for contact correspondence was sent to the prescriber on 07 May 2014. The prescriber failed to contact the team for re-education by the deadline of 28 May 2014. A Warning letter was submitted to the prescriber on 05 June 2014, requiring

Report No.[1]	Report Description	Report Status	Mitigating Action
	PPAFs. **[36-Month Assessment Report Update]** On 17 April 2014, the prescriber was identified as not submitting PPAFs for 5 new patients who were at least 10 days past enrollment.		that the prescriber submit a Corrective Action Plan by 26 June 2014. A Corrective Action Plan was received on 24 June 2014 stating that the patients with missing PPAFs were not continuing therapy and that moving forward forms would be completed online with each prescription. The plan was approved by the NCRT on 26 June 2014. The prescriber was monitored from 26 June 2014 to 26 July 2014 and the non-compliance case was closed after no further non-compliance cases were identified during this time period. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
	ID#214[2] (Case #12925438 & 20277916) 2013 **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance on 07 May 2013 for not submitting PPAFs. **[36-Month Assessment Report Update]** On 16 June 2014 the prescriber was identified as not submitting PPAFs for 5 new patients who were at least 10 days past enrollment.	**Closed**	The TIRF REMS Access Program re-educated the prescriber on 20 June 2014. The prescriber stated that his office staff should be sending PPAFs after they are completed. He stated that he would have a meeting with his staff to re-educate on proper submission of PPAFs. The prescriber submitted 1 of the 5 outstanding PPAFs. The remaining 4 PPAFs would not be submitted as the patients were identified as not continuing therapy. On 26 June 2014 a second formal Notice for Non-Compliance was issued to the prescriber since this was a repeat offense of enrolling >5 patients without a PPAF by the prescriber. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
	ID#217[2] (Case #12482378 & 20214979) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance on 13 March 2013 for not submitting PPAFs. **[36-Month Assessment Report Update]** On 11 June 2014, the prescriber was identified as not submitting PPAFs for 5 new patients who were at least 10 days past enrollment.	**Closed**	The TIRF REMS Access Program re-educated the prescriber on 17 June 2014. The prescriber stated that he had not submitted the PPAFs as he did not know that he had to submit PPAFs for patients that he would only be seeing one time. The prescriber submitted 4 of the 5 outstanding PPAFs. The last PPAF would not be submitted as the patient was identified as not continuing therapy. A second formal Notice for Non-Compliance was issued to the prescriber on 26 June 2014 since this was a repeat offense of enrolling >5 patients without a PPAF by the prescriber. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.

Report No.[1]	Report Description	Report Status	Mitigating Action
	ID#241[2] (Case #12903118 & 20954331) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance on 17 April 2013 for not submitting PPAFs. **[36-Month Assessment Report Update]** On 08 August 2014, the prescriber was identified as not submitting PPAFs for 5 new patients who were at least 10 days past enrollment.	**Closed**	The TIRF REMS Access Program re-educated the prescriber on 18 August 2014. The prescriber advised that he had not submitted PPAFs as he changed his EMR system and some of the patient data has not converted over. The prescriber stated that his system is now improved and he will be more mindful in the future. The prescriber submitted 4 of the 5 PPAFs. The last outstanding PPAF would not be submitted as the patient was identified as not continuing therapy. A second formal Notice for Non-Compliance was issued to the prescriber on 28 August 2014 since this was a repeat offense of enrolling >5 patients without a PPAF by the prescriber. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
	ID#243 (Case #19074028 & 20954272) On 03 April 2014 the prescriber was identified as not submitting PPAFs for 5 patients. The TIRF REMS Access Program attempted to contact the prescriber multiple times between 04 April 2014 and 09 May 2014. A request for contact was issued to the prescriber after multiple unsuccessful contact attempts. The prescriber failed to contact the program for re-education by the deadline of 30 May 2014. A formal Notice of Non-Compliance was issued to the prescriber on 06 June 2014. None of the 5 outstanding PPAFs were submitted as all patients were identified as not continuing therapy. On 08 August 2014 the prescriber was again identified as not submitting PPAFs for 7 new patients who were at least 10 days past enrollment.	**Closed**	The TIRF REMS Access Program re-educated the prescriber on 27 August 2014. The prescriber stated that her office staff had been submitting completed PPAFs to the pharmacy instead of the TIRF REMS Access Program. She advised that they have corrected the issue and that all PPAFs should be submitted correctly moving forward. The prescriber submitted all 7 outstanding PPAFs. On 04 September 2014 a second formal Notice for Non-Compliance was issued to the prescriber since this was a repeat offense of enrolling >5 patients without a PPAF by the prescriber. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
	ID#249[2] (Case #13861249 & 20761198) **[24-Month Assessment Report Non-Compliance]**	**Closed**	The TIRF REMS Access Program attempted to contact the prescriber multiple times between 31 July 2014 and 11 August 2014. A request for contact correspondence was issued to the prescriber after all attempts for contact were

Report No.[1]	Report Description	Report Status	Mitigating Action
	Prescriber was issued a first formal Notice for Non-Compliance on 13 August 2013 for not submitting PPAFs. **[36-Month Assessment Report Update]** On 24 July 2014, the prescriber was identified for not submitting PPAFs for 8 new patients who were at least 10 days past enrollment.		unsuccessful. The prescriber failed to contact the program for re-education by the deadline of 09 August 2014. The prescriber submitted 1 of the 8 outstanding PPAFs. The remaining 7 PPAFs will not be submitted as the patients were identified as not continuing therapy. The prescriber was re-educated during an inbound call on 18 September 2014. The prescriber stated that the reason he did not submit PPAFs was because he was working at 3 different offices. The prescriber stated that he now works at one location and understands that it is his responsibility to submit a PPAF for each new patient prior to their first prescription. A second formal Notice for Non-Compliance was issued to the prescriber on 25 September 2014 since this was a repeat offense of enrolling >5 patients without a PPAF by the prescriber. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
	ID#250[2] (Case #12903203 & 21174276) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance on 25 April 2013 for not submitting PPAFs. **[36-Month Assessment Report Update]** On 21 August 2014, the prescriber was identified for not submitting PPAFs for 5 new patients who were at least 10 days past enrollment.	**Closed**	The TIRF REMS Access Program re-educated the prescriber on the program requirements on 09 September 2014. The prescriber stated that the reason he did not submit the PPAFs is because he only saw these patients one time. He stated that he now understands that a PPAF is required for each new patient prior to their first prescription regardless of the length of therapy. The prescriber submitted all of the 5 outstanding PPAFs. A second formal Notice for Non-Compliance was issued to the prescriber on 19 September 2014 since this was a repeat offense of enrolling >5 patients without a PPAF by the prescriber. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
	ID#264[2] (Case #13861305 & 21103182) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance on 12 August 2013 for not submitting PPAFs.	**Closed**	The TIRF REMS Access Program attempted to contact the prescriber for re-education multiple times between 20 August 2014 and 08 September 2014. A request for contact was issued to the prescriber after all attempts were unsuccessful. The prescriber failed to contact the program for re-education by the deadline of 02 October 2014. The prescriber did not submit any of the outstanding PPAFs as all 6 patients were identified as not continuing therapy.

Report No.[1]	Report Description	Report Status	Mitigating Action
	[36-Month Assessment Report Update] On 18 August 2014, the prescriber was identified for not submitting PPAFs for 6 new patients who were at least 10 days past enrollment.		A second formal Notice for Non-Compliance was issued to the prescriber on 09 October 2014 since this was a repeat offense of enrolling >5 patients without a PPAF by the prescriber. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
	ID#267[2] (Case #15425426 & 21322228) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance on 11 October 2013 for not submitting PPAFs. **[36-Month Assessment Report Update]** On 02 September 2014, the prescriber was identified as not submitting PPAFs for 6 new patients.		The TIRF REMS Access Program attempted to contact the prescriber multiple times between 02 September 2014 and 15 September 2014. A request for contact correspondence was issued to the prescriber on 18 September 2014 after all attempts to contact were unsuccessful. The prescriber failed to contact the TIRF REMS Access Program for re-education by the deadline of 09 October 2014. The prescriber submitted 2 of the 6 outstanding PPAFs. The remaining 4 PPAFs would not be submitted as those patients were identified as not continuing therapy. A second formal Notice for Non-Compliance was issued to the prescriber on 16 October 2014 since this was a repeat offense of enrolling >5 patients without a PPAF by the prescriber. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
	ID#270 (Case #19220984 & 21275629) On 10 April 2014, the prescriber was identified as not submitting PPAFs for 5 patients. The TIRF REMS Access Program attempted to contact the prescriber multiple times between 11 April 2014 and 28 April 2014. A request for contact was issued on 29 April 2014 after all attempts for contact we unsuccessful. The prescriber failed to contact the program for re-education by the deadline of 20 May 2014. A formal Notice for Non-Compliance was issued to the		The TIRF REMS Access Program attempted to contact the prescriber multiple times between 28 August 2014 and 11 September 2014. A request for contact correspondence was issued to the prescriber after all contact attempts were unsuccessful. The prescriber failed to contact the TIRF REMS Access Program for re-education by the deadline of 07 October 2014. The prescriber submitted none of the 5 outstanding PPAFs as the patients were identified as not continuing therapy. On 17 October 2014 a second formal Notice for Non-Compliance was issued to the prescriber since this was a repeat offense of enrolling >5 patients without a PPAF by the prescriber.

Report No.[1]	Report Description	Report Status	Mitigating Action
	prescriber on 29 May 2014. The prescriber submitted none of the outstanding PPAFs as all patients were identified as not continuing therapy. On 28 August 2014, the prescriber was again identified as not submitting PPAFs for 5 new patients.		Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.

[1] Case was included in the Non-Compliance Activity Reports by Stakeholder Table and as a non-compliance narrative in the 24-Month Report.

[2] Case was included in the Non-Compliance Activity Reports by Stakeholder Table in the 24-Month Report.

7 SAFETY SURVEILLANCE

7.1 Adverse Event Reporting [Metric 29]

TIRF Sponsors process adverse event reports related to their specific products and report to the FDA according to current regulations outlined in 21 CFR 314.80 and the sponsor's respective Standard Operating Procedures (SOPs).

7.2 TRIG Sponsor Adverse Event Data of Interest [Metric 30]

During discussions between the FDA and the TRIG, the FDA requested an aggregate root cause analysis (RCA) be conducted of all spontaneous adverse event reports of addiction, death, overdose, and pediatric exposure from the TIRF Sponsors. Based on this request the TRIG Sponsor companies used a third party, UBC, to conduct this analysis. The sponsors identified the appropriate Medical Dictionary for Drug Regulatory Activities (MedDRA) codes to provide data including narratives or MedWatch forms which UBC summarized based on the FDA's request (see Appendix 12.1). Reports were reviewed and duplicates consolidated. Originally case reports were selected based on the specified Preferred Terms (PTs); upon UBC's review of the narrative information some case reports did not meet the specified criteria and were excluded from the analysis. Additionally, literature reports and reports from Poison Centers were excluded.

Metrics of interest included: the number of event reports in each event category of interest (addiction, death, overdose, pediatric exposures); counts of adverse events related to inappropriate conversions between TIRF products; counts of adverse events related to accidental and unintentional exposures; and counts of adverse events that are associated with use of TIRF medicines in non-opioid tolerant patients. As per the agreement with FDA, the reporting period for this analysis was 29 October 2013 to 28 August 2014 to allow sufficient time to complete this analysis.

There were 367 unique case reports that met the specified criteria. After a review of the 367 MedWatch Forms or narratives, no reports of inappropriate conversions between TIRF products were noted. None of the narratives indicated accidental or unintentional exposures, or non-opioid tolerance.

7.3 Number of Adverse Events of Special Interest

The total number of cases of interest are presented in Table 23 below. Of the 367 cases, 362 (98.6%) had an outcome of death, 4 (1%) were reports of addiction, and 2 (0.5%) were pediatric exposures. There were no reported overdoses. Only one case was included in more than one category: one pediatric exposure had an outcome of death.

Table 23 Number of Cases of Adverse Events of Special Interest

AEs of Interest	Number of Reports	Percentage[a]
Total Number of AEs of Interest	**367**	
Addiction	4	1.1%
Death	362	98.6%
Overdose	0	0
Pediatric Exposure	2	0.5%

[a]Cases may have more than one adverse event of interest.

Table 24 shows the reporting rates for each of the adverse events of special interest using two different denominators. The first denominator is the number of prescriptions for TIRF products in the time period. Rates are expressed per 100,000 prescriptions. The second is the number of patients known to be exposed to TIRF products during the period of interest: 29 October 2013 to 28 August 2014. Rates are expressed per 100,000 exposed population.

Table 24 Rate of Adverse Events by Total Prescriptions and Total Patients

	Number of Adverse Events	Rate of Adverse Events by Prescriptions[a] (N= 94,464)	Rate of Adverse Events by Number of Patients[b] (N= 14,772)
Addiction	4	4.23	27.07
Death	362	383.21	2450.58
Overdose	0	-	-
Pediatric Exposure	2	2.11	13.53

[a]Rates are expressed per 100,000 prescriptions.

[b]Rates are expressed per 100,000 exposed population.

Four cases were classified as cases of addiction. While all four were reported during this reporting period, one case report described events occurring in 2012. Of the four cases, one was considered medically significant and was hospitalized; 1 had an outcome of "not recovered" at the time of the cut off (28 August 2014); 1 had an outcome of "resolved"; and 1 outcome was unknown. Table 25 provides details of these four cases.

Table 25 Cases of Addiction Received from TRIG Sponsors during the Reporting Period: 29 October 2013 - 28 August 2014

	Patient		Date							
UBC ID	Age	Gender	Event	Report	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
1271	71	Male	2014	13MAY2014	Drug dependence, Drug tolerance, Drug withdrawal syndrome, Inappropriate schedule of drug administration	Cancer pain	Unknown	None reported	None reported	Medically Significant, Hospitalized
1285	64	Female	01JAN2014	27MAY2014	Abdominal distension, Adverse reaction, Anxiety, Bedridden, Cardiac discomfort, Device defective, Device issue, Drug dependence, Fear, General physical health deterioration, Muscular weakness, Abdominal distension, Anger, Anxiety, Detoxification, Feeling abnormal, Pain, Spinal disorder, Weight increased	Chronic pain,spinal atrophy,muscular dystrophy	Unknown	Thyroid, Klonopin	None reported	Not Recovered/ Not Resolved

	Patient		Date							
UBC ID	Age	Gender	Event	Report	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
1329	72	Male	01DEC2012	25JUN2014	Haemorrhage intracranial, Headache, Incorrect dosage administered, Musculoskeletal discomfort, Weight decreased	Pain	Unknown	Morphine, Tramadex, Marijuana	None reported	Recovering/ Resolving
1360	54	Male	14JUL2014	14JUL2014	Drug withdrawal syndrome, Intentional drug misuse, Off label use	Back pain, neck pain	2 Years	None reported	None reported	Unknown

The overdose table below represents a group of MedWatch forms generated as the result of one reporter notifying one sponsor of 23 cases of overdose and diversion.

In early November 2013, The National Association of Drug Diversion Investigators (NADDI) contacted a TIRF sponsor company indicating over twenty overdoses occurred in one county over a 5 day period. NADDI reported there had been 2 deaths and one person was in critical condition. In some cases Narcan (naloxone hydrochloride injection) was used in the field to save lives. Two arrests had been made and over one ounce of fentanyl was seized. In the days following this initial report, NADDI contacted the sponsor again to provide an update on the total number of cases and the suspect fentanyl seized. They reported a total of 23 overdoses, three which resulted in death. The fentanyl seized was off- white and somewhat chunky in consistency similar to powder cocaine. Upon investigation, NADDI noted that they do not feel this was a drug diversion as there were high quantities and no recent fentanyl thefts had been reported. The substance was sold in sandwich bags as 1-1.5 ounces as heroin but when tested was found to be fentanyl. NADDI stated they felt this fentanyl was made in a lab in the southwest US or across the border.

While these cases do not meet the requirements for reporting within this REMS assessment, the sponsor has chosen to include these cases as the initial report could not rule out fentanyl as the substance in question. These reports are not included in the counts of cases of adverse events of interest or in the prescription and population rates because it is clear that a TIRF product was not involved.

Table 26 Cases of Overdose Received from TRIG Sponsors during the Reporting Period: 29 October 2013 - 28 August 2014

	Patient		Date							
UBC ID	Age	Gender	Event	Report	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
1038	UNK	Male	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Death
1039	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	2 Years	None reported	None reported	Death
1040	UNK	Unknown	01NOV2013	20NOV2013	Brain death, Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Death
1041	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1042	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1043	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1044	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1045	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1046	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1047	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1048	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1049	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1050	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1051	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown

	Patient		Date							
UBC ID	Age	Gender	Event	Report	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
1052	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1053	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1054	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1055	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1056	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1057	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1058	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1059	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown
1060	UNK	Unknown	01NOV2013	20NOV2013	Drug diversion, Overdose	Unknown	Unknown	None reported	None reported	Unknown

The data provided by the six TRIG sponsors showed 362 cases with an outcome of death (Table 27). Of those, 223 (62%) had a preferred term of death with no cause of death indicated, 83 (23%) cases had a preferred term of a malignancy (cancer, carcinoma, myeloma, metastatic, lymphoma, glioblastoma, leukemia, neoplasm). There was one case with the term “mass” reported as the preferred term. Respiratory failure and respiratory depression appear as preferred terms for five cases. Six (2%) cases have a preferred term of cardiac death, cardiac arrest or myocardial infarction.

One case (0.3%) of death was a result of suicide. The reporter indicated that the patient committed suicide due to pain after stopping fentanyl.

Forty seven of the 362 reported deaths were identified through the TIRF REMS Access Programs PPAF renewal process. That is, during the outreach to the prescribers’ offices to request a PPAF renewal, the program learned of 47 patient deaths.

Table 27 Cases of Death Received from TRIG Sponsors during the Reporting Period: 29 October 2013 - 28 August 2014

	Patient		Date							
UBC ID	Age	Gender	Event	Report	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
1001	67	Female	01OCT2013	29OCT2013	Death, Adverse event	Pain	Unknown	None reported	None reported	Death
1002	50	Male	01JAN2013	29OCT2013	Death, Adverse event	Unknown	Unknown	None reported	None reported	Death
1003	66	Male	29JUN2013	29OCT2013	Death	Cancer pain	2013-06-12 - 2013-06-29	Oxycodone	None reported	Death
1004	62	Female	Unknown	29OCT2013	Death	Unknown	Unknown	None reported	None reported	Death
1005	41	Female	2013	29OCT2013	Disease progression	Unknown	Unknown	None reported	None reported	Death
1006	78	Male	2013	29OCT2013	Death	Unknown	Unknown	None reported	None reported	Death
1007	57	Female	07OCT2013	30OCT2013	Death	Unknown	Unknown	None reported	None reported	Death
1008	UNK	Female	Unknown	30OCT2013	Death	Cancer pain	2013-06-12 - UNK	None reported	None reported	Death
1009	UNK	Male	Unknown	30OCT2013	Death	Cancer pain	2013-06-12 - UNK	None reported	None reported	Death
1010	UNK	Female	Unknown	30OCT2013	Death	Cancer pain	2013-06-12 - UNK	None reported	None reported	Death
1011	UNK	Male	Unknown	30OCT2013	Death	Cancer pain	2013-06-12 - UNK	None reported	None reported	Death
1012	UNK	Male	Unknown	30OCT2013	Death	Cancer pain	2013-06-12 - UNK	None reported	None reported	Death
1013	UNK	Female	Unknown	30OCT2013	Death	Cancer pain	2013-06-12 - UNK	None reported	None reported	Death
1014	48	Female	Unknown	30OCT2013	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1015	52	Male	Unknown	01NOV2013	Neoplasm malignant, Treatment noncompliance	Unknown	Unknown	None reported	None reported	Death
1016	69	Female	Unknown	01NOV2013	Disease progression, Treatment noncompliance	Unknown	2 Years	None reported	None reported	Death
1017	54	Male	Unknown	01NOV2013	Neoplasm malignant	Unknown	Unknown	None reported	None reported	Death
1018	73	Female	2013	01NOV2013	Disease progression	Unknown	Unknown	None reported	None reported	Death
1019	64	Male	Unknown	04NOV2013	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1020	62	Male	Unknown	14NOV2013	Death	Unknown	Unknown	None reported	None reported	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1021	78	Female	01JAN2013	14NOV2013	Cardiac arrest, Conduction disorder, Lethargy, Respiratory arrest, Respiratory depression, Somnolence	Unknown	Unknown	None reported	Fentanyl Patch, Hydromorphone	Death
1025	59	Female	01JAN2013	14NOV2013	Acidosis, Blood creatinine increased, Cardiac arrest, Coma, Hypotension, Hypothermia, Renal failure, Respiratory depression	Unknown	Unknown	None reported	Fentanyl Patch	Death
1031	51	Female	Unknown	18NOV2013	Death	Unknown	Unknown	None reported	None reported	Death
1032	64	Male	Unknown	18NOV2013	Death	Unknown	Unknown	None reported	None reported	Death
1033	50	Female	Unknown	18NOV2013	Death	Unknown	Unknown	None reported	None reported	Death
1034	60	Male	01JAN2011	18NOV2013	Death, Drug prescribing error	Unknown	Unknown	None reported	None reported	Death
1035	UNK	Male	Unknown	18NOV2013	Death	Unknown	Unknown	None reported	None reported	Death
1036	64	Female	10NOV2013	19NOV2013	Death	Unknown	Unknown	None reported	None reported	Death
1037	53	Female	25MAR2012	19NOV2013	Death	Rectal cancer	Unknown	Adderall, Dilaudid, Lorazepam, Oxycontin, Wellbutrin, Zanaflex	None reported	Death
1061	65	Female	01JAN2013	22NOV2013	Drug ineffective, Cardiac arrest, Death, Malignant neoplasm progression, Myocardial infarction, Pain, Systemic lupus erythematosus	Breakthrough cancer pain	Unknown	Oxycontin, Oxy IR, Duragesic, Methadone, Vicodin	None reported	Death
1062	35	Male	Unknown	26NOV2013	Death, Treatment noncompliance	Unknown	Unknown	None reported	None reported	Death
1063	41	Female	05NOV2013, 01OCT2013	03DEC2013	Death, Adverse event, Hospitalisation	Breakthrough cancer pain	Unknown	Fentanyl, Roxanol	None reported	Death
1064	69	Male	Unknown	06DEC2013	Neoplasm malignant	Cancer pain	Unknown	None reported	None reported	Death
1065	UNK	Unknown	2013	09DEC2013	Death	Unknown	Unknown	None reported	None reported	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1066	75	Male	Unknown	12DEC2013	Death	Unknown	Unknown	None reported	None reported	Death
1067	40	Male	30OCT2013, 01OCT2013	12DEC2013	Death, Unresponsive to stimuli	Unknown	Unknown	None reported	None reported	Death
1068	63	Male	01JAN2013	13DEC2013	Death	Unknown	Unknown	None reported	None reported	Death
1069	55	Female	Unknown	19DEC2013	Disease progression, Treatment noncompliance	Unknown	Unknown	None reported	None reported	Death
1070	58	Female	Unknown	27DEC2013	Death	Unknown	Unknown	None reported	None reported	Death
1071	76	Male	Unknown	31DEC2013	Adverse event, Disease progression, Plasma cell myeloma	Unknown	Unknown	None reported	None reported	Death
1072	50	Male	Unknown	31DEC2013	Disease progression, Glioblastoma, Hospice care	Unknown	Unknown	None reported	None reported	Death
1073	47	Female	Unknown	31DEC2013	Adverse event, Metastases to peritoneum	Unknown	Unknown	None reported	None reported	Death
1074	56	Female	Unknown	31DEC2013	Colon cancer metastatic, Hospice care	Unknown	18 Days	None reported	None reported	Death
1075	44	Male	Unknown	31DEC2013	Glioblastoma, Hospice care	Unknown	Unknown	None reported	None reported	Death
1076	72	Female	Unknown	31DEC2013	Hospice care, Lymphoma	Unknown	Unknown	None reported	None reported	Death
1077	47	Male	Unknown	31DEC2013	Brain neoplasm, Hospice care	Unknown	Unknown	None reported	None reported	Death
1078	63	Male	Unknown	31DEC2013	Aspergillus infection	Unknown	Unknown	None reported	None reported	Death
1079	58	Male	05APR2012	02JAN2014	Anal cancer, Adverse event	Breakthrough cancer pain	Unknown	None reported	None reported	Death
1080	52	Male	10AUG2013	02JAN2014	Adverse event, Neoplasm malignant, Drug ineffective	Breakthrough cancer pain	Unknown	None reported	None reported	Death
1081	70	Male	Unknown	02JAN2014	Disease progression	Unknown	Unknown	None reported	None reported	Death
1082	45	Male	Unknown	03JAN2014	Death	Unknown	1 Months	None reported	None reported	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1083	67	Female	20DEC2013, 17DEC2013	03JAN2014	Death, Sepsis, Lung neoplasm malignant	Unknown	Unknown	None reported	None reported	Death
1086	41	Male	03JAN2014	13JAN2014	Cardiac arrest, Death	Cancer	2013-04-23 - UNK	Dilaudid	None reported	Death
1087	47	Female	13NOV2013, 11SEP2013, 11SEP2013, 11SEP2013, 11SEP2013	22JAN2014	Death, Central nervous system lesion, Hepatic encephalopathy, Hepatic failure, Malaise	Metastatic pain-neoplasma related pain	Unknown	Ms Contin, Hydrocodone, Lorazepam, Lomotil, Remeron	None reported	Death
1088	61	Female	02JAN2014	23JAN2014	Encephalopathy, Respiratory failure	Breakthrough cancer pain	Unknown	Oxycontin, Oxycodone, Lorazepam, Levothyroxine, Vitamin D3, Flonase, Triamcinolone	None reported	Death
1089	53	Male	Unknown	24JAN2014	Death	Cancer pain	Unknown	None reported	None reported	Death
1090	49	Female	Unknown	28JAN2014	Death	Breakthrough cancer pain	Unknown	Fentanyl	None reported	Death
1092	59	Male	Unknown	03FEB2014	Death	Unknown	Unknown	None reported	None reported	Death
1093	UNK	Female	MAR2012	06FEB2014	Disease progression	Unknown	Unknown	None reported	None reported	Death
1094	54	Female	Unknown	14FEB2014	Death	Unknown	Unknown	None reported	None reported	Death
1095	69	Female	Unknown	17FEB2014	Death	Unknown	Unknown	None reported	None reported	Death
1096	57	Female	28FEB2013	17FEB2014	Death	Unknown	Unknown	None reported	None reported	Death
1097	78	Female	Unknown	18FEB2014	Death	Lung cancer	Unknown	Hydromorphone, Clonidine, Baclofen, Bupivacaine, Dilaudid, Methadone	None reported	Death
1098	77	Female	01JAN2013	18FEB2014	Death	Unknown	Unknown	None reported	None reported	Death
1099	54	Female	Unknown	20FEB2014	Breast cancer, Lung carcinoma cell type unspecified stage IV	Unknown	Unknown	None reported	None reported	Death
1100	51	Female	Unknown	20FEB2014	Death	Unknown	Unknown	None reported	None reported	Death
1101	49	Male	28APR2012	20FEB2014	Death	Unknown	Unknown	None reported	None reported	Death
1102	77	Male	Unknown	20FEB2014	Death	Unknown	Unknown	None reported	None reported	Death
1103	70	Male	11JUN2013	20FEB2014	Death	Cancer pain	Unknown	None reported	Fentanyl Citrate	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1104	79	Female	Unknown	20FEB2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1105	54	Female	Unknown	21FEB2014	Death	Unknown	Unknown	None reported	None reported	Death
1106	69	Male	Unknown	24FEB2014	Renal cancer	Pain	Unknown	None reported	None reported	Death
1108	59	Female	Unknown	24FEB2014	Death	Unknown	Unknown	None reported	None reported	Death
1109	UNK	Female	Unknown	24FEB2014	Death	Pain management	Unknown	None reported	None reported	Death
1110	UNK	Female	Unknown	25FEB2014	Death	Unknown	Unknown	None reported	Copaxone	Death
1111	UNK	Male	Unknown	26FEB2014	Death	Unknown	Unknown	None reported	None reported	Death
1112	59	Male	Unknown	26FEB2014	Death	Unknown	Unknown	None reported	None reported	Death
1113	53	Female	18APR2012	26FEB2014	Death	Metastatic neoplasm	Unknown	None reported	Fentanyl Citrate	Death
1114	69	Female	09AUG2013	27FEB2014	Hospice care, Death	Unknown	Unknown	Clonazepam, Senna-S, Fentanyl, Fluoxetine, Ibuprofen, Megace, Metoprolol, Olanzapine, Warfarin	None reported	Death
1115	57	Female	Unknown	27FEB2014	Breast cancer metastatic	Unknown	2 Years	Tylenol, Albuterol, Anastrozole, Cetirizine, Clonazepam, Senna S, Hydroxyzine, Humalog, Lactulose, Lidoderm, Milk of Magnesia, Naproxen, Oxycodone, Oxycontin, Miralax	None reported	Death
1116	48	Female	Unknown	27FEB2014	Death	Unknown	Unknown	None reported	None reported	Death
1117	60	Female	Unknown	28FEB2014	Lung cancer metastatic	Unknown	Unknown	None reported	None reported	Death
1118	66	Female	Unknown	28FEB2014	Death	Unknown	Unknown	None reported	None reported	Death
1119	60	Male	Unknown	28FEB2014	Colon cancer stage IV	Breakthrough cancer pain	Unknown	None reported	None reported	Death
1120	57	Female	16APR2012	28FEB2014	Death	Unknown	Unknown	None reported	None reported	Death
1121	60	Female	22MAY2012	28FEB2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1122	74	Female	24JUL2012	28FEB2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1123	45	Female	18NOV2013, 09AUG2013	04MAR2014	Femur fracture, Mass, Fracture, Bone cancer, Breast cancer metastatic, Fall, Hospitalisation, Osteoarthritis	Metastatic lesion pain	Unknown	Oxycontin, Synthroid, Robaxin, Dilaudid, Lasix, Chemotherapeutics NOS, Lisionopril, Oxycodone	None reported	Death
1124	62	Female	Unknown	04MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1125	79	Female	Unknown	04MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1126	UNK	Female	Unknown	04MAR2014	Disease progression, Pancreatic carcinoma metastatic	Cancer pain	2014-02-26 - UNK	None reported	None reported	Death
1127	58	Female	02DEC2013	04MAR2014	Metastatic neoplasm	Cancer pain	Unknown	None reported	None reported	Death
1128	52	Female	Unknown	05MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1129	UNK	Male	Unknown	05MAR2014	Death	Unknown	2014-02-26 - UNK	None reported	None reported	Death
1130	UNK	Unknown	Unknown	05MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1131	79	Female	2013	05MAR2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1133	UNK	Female	01JAN2012	06MAR2014	Death, Feeling abnormal, Unresponsive to stimuli	Unknown	Unknown	None reported	None reported	Death
1134	69	Female	Unknown	06MAR2014	Neoplasm malignant	Breakthrough pain	Unknown	Roxicodone	None reported	Death
1135	58	Female	Unknown	06MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1136	UNK	Female	Unknown	06MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1137	UNK	Female	Unknown	06MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1138	39	Female	11NOV2012	06MAR2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1139	53	Male	Unknown	07MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1140	83	Male	Unknown	10MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1141	66	Male	Unknown	10MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1142	68	Female	Unknown	10MAR2014	Disease recurrence	Unknown	Unknown	None reported	None reported	Death
1143	64	Male	Unknown	11MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1144	75	Male	Unknown	11MAR2014	Neoplasm malignant	Unknown	Unknown	None reported	None reported	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1145	31	Male	Unknown	11MAR2014	Crohn's disease, Off label use	Chronic and severe crohn's disease of small and large intest	Unknown	Stargesic	None reported	Death
1146	60	Male	Unknown	11MAR2014	Death	Colon cancer pain	Unknown	Oxycontin	None reported	Death
1147	48	Female	19MAY2012	12MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1148	48	Female	Unknown	12MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1149	UNK	Female	Unknown	13MAR2014	Death	Pain	Unknown	None reported	None reported	Death
1150	59	Male	JUL2012	13MAR2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1152	75	Male	01DEC2012	17MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1153	48	Male	04JUN2013	17MAR2014	Neoplasm Progression	Unknown	Unknown	None reported	None reported	Death
1155	53	Female	21MAR2013	17MAR2014	Neoplasm Progression	Cancer pain	Unknown	None reported	None reported	Death
1156	54	Female	20DEC2013	17MAR2014	Death	Unknown	12/9/2013-UNK	None reported	None reported	Death
1158	66	Male	05MAY2012	17MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1159	UNK	Female	Unknown	17MAR2014	Drug Ineffective/Death	Breakthrough cancer pain	Unknown	None reported	None reported	Unknown[a]
1160	62	Male	15SEP2013	17MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1161	64	Female	AUG2012	17MAR2014	Neoplasm Progression	Cancer pain	Unknown	None reported	None reported	Death
1162	UNK	Female	Unknown	17MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1163	42	Male	Unknown	18MAR2014	Glioblastoma multiforme	Unknown	Unknown	None reported	None reported	Death
1164	65	Female	Unknown	18MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1165	UNK	Male	Unknown	18MAR2014	Death	Prostate cancer	2014-02-26 - UNK	None reported	None reported	Death
1166	UNK	Female	Unknown	18MAR2014	Death	Cancer pain	2014-02-26 - UNK	None reported	None reported	Death
1167	60	Female	SEP2013	19MAR2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1168	59	Female	18MAR2014, 15MAR2014	20MAR2014	Chronic obstructive pulmonary disease, Hypotension, Sepsis, Pneumonia, Acute respiratory failure	Metastatic lung cancer	Unknown	None reported	None reported	Death
1169	81	Male	01JAN2013	20MAR2014	Death	Unknown	Unknown	None reported	None reported	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1170	UNK	Female	Unknown	20MAR2014	Neoplasm malignant	Unknown	2014-02-26 - UNK	None reported	None reported	Death
1171	UNK	Male	Unknown	20MAR2014	Death, Drug effect decreased	Breakthrough cancer pain	2014-02-26 - UNK	Morphine	None reported	Death
1172	39	Female	Unknown	21MAR2014	Malaise	Breakthrough cancer pain	Unknown	None reported	None reported	Death
1173	75	Female	Unknown	21MAR2014	Lung cancer metastatic	Breakthrough pain	1 Years	None reported	Percocet	Death
1175[b]	0.7	Unknown	Unknown	24MAR2014	Death, Off label use	Unknown	Unknown	None reported	None reported	Death
1176	55	Male	11JUN2012	24MAR2014	Death	Unknown	1 Weeks	None reported	None reported	Death
1177	68	Male	27APR2012	24MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1178	UNK	Female	Unknown	25MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1179	59	Female	Unknown	25MAR2014	Renal cancer	Unknown	Unknown	None reported	None reported	Death
1180	51	Male	Unknown	25MAR2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1182	61	Male	Unknown	27MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1183	46	Male	01JAN2013	27MAR2014	Myocardial infarction	Unknown	Unknown	None reported	None reported	Death
1185	53	Female	Unknown	27MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1186	59	Male	Unknown	27MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1187	UNK	Male	Unknown	27MAR2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1188	43	Female	Unknown	27MAR2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1189	59	Male	Unknown	27MAR2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1190	63	Female	Unknown	27MAR2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1191	UNK	Female	Unknown	28MAR2014	Disease progression	Unknown	Unknown	None reported	None reported	Death
1192	UNK	Female	Unknown	28MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1193	54	Male	06JAN2014, 01DEC2012, 01NOV2012, 01NOV2012, 01APR2012	31MAR2014	Neoplasm malignant, Pain, Herpes zoster, Polyneuropathy, Cholecystitis	Breakthrough cancer pain	Unknown	Gabapentin, Dilaudid	None reported	Death
1194	UNK	Female	Unknown	31MAR2014	Death	Unknown	Unknown	None reported	None reported	Death
1195	62	Unknown	Unknown	01APR2014	Endometrial cancer metastatic	Breakthrough cancer pain	Unknown	None reported	None reported	Death
1196	UNK	Unknown	Unknown	03APR2014	Death	Unknown	Unknown	None reported	None reported	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1197	UNK	Unknown	Unknown	07APR2014	Death	Pain due to cancer	2 Years	None reported	None reported	Death
1198	61	Male	Unknown	07APR2014	Death	Unknown	Unknown	None reported	None reported	Death
1199	63	Male	Unknown	07APR2014	Death	Unknown	Unknown	None reported	None reported	Death
1200	60	Male	Unknown	07APR2014	Death	Unknown	Unknown	None reported	None reported	Death
1201	47	Male	Unknown	07APR2014	Colon cancer	Unknown	Unknown	None reported	None reported	Death
1202	34	Female	Unknown	07APR2014	Ocular cancer metastatic, Ocular neoplasm	Unknown	Unknown	None reported	None reported	Death
1203	54	Male	30APR2012	07APR2014	Colon Cancer, Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1204	46	Female	Unknown	07APR2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1205	60	Male	Unknown	07APR2014	H1N1 Influenza, Death, Renal Failure Acute, Atelectasis, Pneumonia Pseudomonal, Decubitus Ulcer, Neuralgia, Respiratory Failure, Myalgia, Anxiety, Diarrhea, Abdominal Pain	Breakthrough pain	Unknown	Advair, Aluminum Hydroxide-Magnesium Hydroxide-Simethicone, benadryl, Bisacodyl, Daliresp, Ensure Plus, fluconazole, Hydrocortisone, Ipratropium/Albuterol, Iron-B12-Vitamins, Ketoconazole, Levofloxacin, Levothyroxine, Loratadine, Methadone, Mucinex, Nexium, Oxycodone, Silver Sulfadiazine, Singulair, Xanax, Xylocaine, Zomig	Fentanyl Citrate, Clonazepam, Dexamethasone, Polyethylene Glycol 3350	Death
1206	72	Female	Unknown	07APR2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1208	65	Male	Unknown	08APR2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1209	73	Female	Unknown	08APR2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1210	31	Male	01JAN2012	10APR2014	Death	Unknown	Unknown	None reported	None reported	Death
1211	54	Female	Unknown	10APR2014	Disease progression	Unknown	Unknown	None reported	None reported	Death
1212	46	Female	Unknown	11APR2014	Death	Unknown	Unknown	None reported	None reported	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1213	UNK	Female	Unknown	11APR2014	Death	Unknown	2012-08-11 - UNK	None reported	None reported	Death
1214	70	Male	2013	11APR2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1215	46	Female	Unknown	14APR2014	Death	Unknown	Unknown	None reported	None reported	Death
1216	71	Female	Unknown	14APR2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1217	UNK	Female	Unknown	15APR2014	Drug ineffective, Neoplasm progression	Unknown	2012-07-31 - 2012-08-14	None reported	None reported	Death
1218	45	Female	Unknown	15APR2014	Death	Unknown	Unknown	None reported	None reported	Death
1219	61	Female	Unknown	16APR2014	Death	Unknown	Unknown	None reported	None reported	Death
1220	54	Male	06JUL2012	17APR2014	Death	Unknown	Unknown	None reported	None reported	Death
1221	51	Female	01APR2013	17APR2014	Death	Unknown	Unknown	None reported	None reported	Death
1222	75	Female	Unknown	17APR2014	Endometrial cancer metastatic	Breakthrough cancer pain	Unknown	Dilaudid, Fentanyl	None reported	Death
1223	71	Male	Unknown	17APR2014	Breast cancer metastatic	Unknown	Unknown	None reported	None reported	Death
1224	UNK	Female	Unknown	17APR2014	Death	Unknown	2012-07-31 - UNK	None reported	None reported	Death
1225	58	Female	Unknown	17APR2014	Disease progression	Cancer pain	Unknown	None reported	None reported	Death
1226	57	Female	Unknown	18APR2014	Death	Unknown	Unknown	None reported	None reported	Death
1227	66	Male	Unknown	18APR2014	Death	Cancer pain	Unknown	None reported	None reported	Death
1228	49	Female	Unknown	21APR2014	Adenomatous polyposis coli	Unknown	Unknown	None reported	None reported	Death
1229	UNK	Female	Unknown	21APR2014	Death	Unknown	Unknown	None reported	None reported	Death
1230	48	Female	Unknown	22APR2014	Death	Unknown	Unknown	None reported	None reported	Death
1231	51	Male	10JUL2012	22APR2014	Death	Indication not specified	Unknown	None reported	None reported	Death
1232	UNK	Male	Unknown	22APR2014	Disease progression	Breakthrough pain	2012-05 - UNK	Hydrocodone, Lorazepam, Nucynta, Zofran	None reported	Death
1233	62	Male	Unknown	22APR2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1234	28	Male	Unknown	23APR2014	Sepsis, Disease progression	Cancer pain	Unknown	None reported	None reported	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1235	70	Female	Unknown	24APR2014	Cardiac amyloidosis	Unknown	Unknown	Dexamethazon, Levothyroxine, Nexium, Potassium, Calcium, Carafate	None reported	Death
1236	92	Female	Unknown	24APR2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1237	73	Male	Unknown	25APR2014	Death	Unknown	Unknown	None reported	None reported	Death
1238	64	Male	16JUN2013	25APR2014	Death	Unknown	Unknown	None reported	None reported	Death
1239	39	Female	Unknown	27APR2014	Death, Malaise	Unknown	Unknown	None reported	None reported	Death
1240	52	Male	Unknown	28APR2014	Death	Unknown	Unknown	None reported	None reported	Death
1241	59	Male	Unknown	29APR2014	Tracheal cancer	Pain from malignant neoplasm	Unknown	None reported	None reported	Death
1242	80	Female	25NOV2013	29APR2014	Death	Breakthrough cancer pain	11/01/2013-UNK	Fentanyl Patch, Oxycodone, Hydrocodone/Acetaminophen	None reported	Death
1243	83	Female	MAY2012	29APR2014	Death	Unknown	Unknown	None reported	None reported	Death
1244	UNK	Male	Unknown	30APR2014	Death	Unknown	2012-05 - UNK	None reported	None reported	Death
1245	49	Male	Unknown	01MAY2014	Death	Unknown	Unknown	None reported	None reported	Death
1246	76	Male	31AUG2012	01MAY2014	Death	Unknown	Unknown	None reported	None reported	Death
1247	40	Female	07JUN2012	01MAY2014	Neoplasm Progression	Pain	4/19/2012-UNK	Lortab (Hydrocodone/Acetaminophen), Fentanyl Patch, Compazine (Prochlorperazine), Xanax (Alprasolam), Wellbutrin (Bupropion), Omeprazole	None reported	Death
1248	79	Male	Unknown	01MAY2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1249	52	Male	16MAR2012	02MAY2014	Neoplasm Progression	Pain with lung cancer	Unknown	None reported	None reported	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1250	UNK	Male	Unknown	02MAY2014	Neoplasm progression	Breakthrough cancer pain	2013-12-12 - UNK	Aspirin, Clonazepam, Cymbalta, Durabac, Lopressor, Lyrica, Oxycodone, Plaquenil, Spiriva, Zanaflex	None reported	Death
1251	77	Female	31MAY2012	05MAY2014	Death	Unknown	Unknown	None reported	None reported	Death
1252	65	Male	03SEP2012	06MAY2014	Death	Unknown	2013-12-12 - UNK	None reported	None reported	Death
1253	UNK	Male	Unknown	07MAY2014	Application site irritation, Neoplasm progression	Cancer pain	2013-12-12 - UNK	None reported	None reported	Death
1254	47	Male	Unknown	07MAY2014	Pancreatic carcinoma metastatic	Cancer pain	Unknown	None reported	None reported	Death
1255	UNK	Male	Unknown	07MAY2014	Death	Unknown	Unknown	None reported	None reported	Death
1256	65	Male	Unknown	08MAY2014	Death	Unknown	Unknown	None reported	None reported	Death
1257	61	Male	Unknown	08MAY2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1258	38	Female	Unknown	09MAY2014	Death	Unknown	Unknown	None reported	None reported	Death
1259	54	Female	04FEB2013	09MAY2014	Mass, Death	Chronic low back pain	Unknown	Phenergan, Soma, Restoril, Fiorinal, Avinza, Xanax	None reported	Death
1260	47	Female	Unknown	09MAY2014	Death	Unknown	Unknown	None reported	None reported	Death
1261	UNK	Unknown	Unknown	09MAY2014	Death	Unknown	Unknown	None reported	None reported	Death
1262	46	Female	06APR2013	09MAY2014	Death	Unknown	Unknown	None reported	None reported	Death
1263	UNK	Female	Unknown	09MAY2014	Neoplasm progression	Cancer pain	2013-12-12 - UNK	Ms-Contin, Percoset	None reported	Death
1264	UNK	Male	Unknown	09MAY2014	Renal failure	Chronic pain	2013-12-12 - UNK	None reported	None reported	Death
1266	UNK	Female	Unknown	12MAY2014	Death	Unknown	2013-04 - UNK	None reported	None reported	Death
1267	57	Female	Unknown	12MAY2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1268	62	Female	Unknown	13MAY2014	Death	Unknown	Unknown	None reported	None reported	Death
1269	73	Female	Unknown	13MAY2014	Lung cancer metastatic	Severe pain from metastatic lung cancer	Unknown	None reported	None reported	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1270	UNK	Female	Unknown	13MAY2014	Death	Pancreatic cancer	2012-06-29 - UNK	None reported	None reported	Death
1272	UNK	Female	Unknown	13MAY2014	Endometrial cancer metastatic, Ovarian cancer metastatic	Cancer pain	Unknown	None reported	None reported	Death
1273	64	Male	14JUN2012	13MAY2014	Death	Unknown	Unknown	None reported	None reported	Death
1274	UNK	Female	Unknown	14MAY2014	Disease progression, Systemic lupus erythematosus	Pain due to cancer	Unknown	None reported	None reported	Death
1275	44	Male	Unknown	14MAY2014	Death	Colon cancer pain	Unknown	None reported	None reported	Death
1276	77	Female	Unknown	15MAY2014	Death	Malignant neoplasm metastatic to bone	Unknown	None reported	None reported	Death
1277	52	Female	20JAN2014	16MAY2014	Metastatic neoplasm	Cancer pain	Unknown	Methadone, Various Other Medications	None reported	Death
1278	65	Female	Unknown	16MAY2014	Death	Unknown	Unknown	None reported	None reported	Death
1279	UNK	Male	Unknown	16MAY2014	Myocardial infarction	Unknown	Unknown	None reported	None reported	Death
1280	31	Unknown	Unknown	16MAY2014	Death	Unknown	Unknown	None reported	None reported	Death
1281	UNK	Male	Unknown	19MAY2014	Death	Cancer pain	2014-04-21 - UNK	Morphine, Percocet	None reported	Death
1282	UNK	Male	Unknown	22MAY2014	Neoplasm progression	Unknown	2014-04-21 - UNK	None reported	None reported	Death
1284	50	Female	Unknown	23MAY2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1286	39	Male	Unknown	27MAY2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1287	62	Female	Unknown	28MAY2014	Death	Unknown	Unknown	None reported	None reported	Death
1288	55	Female	Unknown	29MAY2014	Death	Unknown	5 Months	None reported	None reported	Death
1289	UNK	Unknown	Unknown	29MAY2014	Death	Unknown	Unknown	None reported	None reported	Death
1290	67	Female	Unknown	29MAY2014	Death	Unknown	5 Months	None reported	None reported	Death
1291	UNK	Unknown	Unknown	30MAY2014	Death	Unknown	Unknown	None reported	None reported	Death
1292	UNK	Male	Unknown	30MAY2014	Neoplasm malignant	Cancer pain	Unknown	None reported	None reported	Death
1293	54	Female	27MAY2014, 23MAY2014	30MAY2014	Breast cancer metastatic, Dyspnoea	Unknown	Unknown	None reported	None reported	Death
1294	62	Male	16JUL2013	30MAY2014	Neoplasm malignant	Unknown	Unknown	None reported	None reported	Death
1296	47	Female	Unknown	02JUN2014	Neoplasm malignant	Unknown	Unknown	None reported	None reported	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1297	54	Female	Unknown	02JUN2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1298	23	Female	Unknown	03JUN2014	Aicardi's syndrome, Off label use	Drug use for unapproved indication,aicardi syndrome	Unknown	None reported	None reported	Death
1299	73	Female	01JAN2012	03JUN2014	Death	Unknown	Unknown	None reported	None reported	Death
1300	62	Female	Unknown	03JUN2014	Breast cancer metastatic	Pain related to metastatic breast cancer	Unknown	None reported	None reported	Death
1301	29	Female	01MAY2014	03JUN2014	Death, Hospice care	Breakthrough cancer pain	Unknown	Lyrica, Norco, Hydrocodone, Gabapentin, Morphine, Metoclopramide, Prilosec	None reported	Death
1302	UNK	Unknown	Unknown	03JUN2014	Death	Unknown	2013-04 - UNK	None reported	None reported	Death
1303	UNK	Female	Unknown	03JUN2014	Dysarthria, Death, Drug ineffective, Memory impairment, Periorbital oedema	Cancer pain, pain	Unknown	Valium, Klor-Con, Cymbalta, Percocet, Duragesic	Prednisone, Hydromorphone, Oxycontin	Death
1304	51	Male	Unknown	06JUN2014	Death	Pain	Unknown	Voltaren Gel, Duragesic, Msir	None reported	Death
1305	62	Female	Unknown	06JUN2014	Prostate cancer metastatic	Breakthrough pain	Unknown	Fentanyl Patch	None reported	Death
1306	42	Male	Unknown	06JUN2014	Death	Unknown	Unknown	None reported	None reported	Death
1308	UNK	Male	Unknown	09JUN2014	Death	Unknown	Unknown	None reported	None reported	Death
1309	UNK	Female	Unknown	11JUN2014	Death	Unknown	Unknown	None reported	None reported	Death
1311	51	Female	Unknown	11JUN2014	Death	Unknown	Unknown	None reported	None reported	Death
1312	58	Female	Unknown	11JUN2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1313	48	Female	Unknown	12JUN2014	Death	Unknown	Unknown	None reported	None reported	Death
1314	UNK	Unknown	Unknown	12JUN2014	Condition aggravated	Cancer pain	Unknown	None reported	None reported	Death
1315	72	Female	12JUN2014	13JUN2014	Death	Unknown	Unknown	None reported	None reported	Death
1316	UNK	Male	2012	13JUN2014	Death	Unknown	UNK - 2012	None reported	None reported	Death
1317	40	Female	20JUL2013	16JUN2014	Condition aggravated	Cancer pain	Unknown	None reported	None reported	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1318	22	Male	Unknown	17JUN2014	Occupational Exposure to Product, Circulatory Collapse, Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1319	61	Female	29OCT2013	18JUN2014	Disease progression	Breakthrough pain	Unknown	None reported	None reported	Death
1320	76	Male	Unknown	18JUN2014	Colon Cancer, Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1321	UNK	Female	Unknown	19JUN2014	Death	Unknown	Unknown	None reported	None reported	Death
1322	UNK	Male	Unknown	19JUN2014	Cardiac death, Off label use	Pain	2012-08-16 - UNK	None reported	None reported	Death
1323	61	Male	Unknown	24JUN2014	Lung neoplasm malignant	Pain	Unknown	None reported	None reported	Death
1324	UNK	Female	Unknown	24JUN2014	Disease progression	Unknown	Unknown	None reported	None reported	Death
1325	UNK	Female	Unknown	24JUN2014	Death	Unknown	Unknown	None reported	None reported	Death
1326	UNK	Male	Unknown	24JUN2014	Death	Unknown	Unknown	None reported	None reported	Death
1327	UNK	Female	Unknown	24JUN2014	Neoplasm progression	Cancer pain	Unknown	None reported	None reported	Death
1328	UNK	Female	Unknown	24JUN2014	Death, Off Label Use	Preoperative care	Unknown	None reported	Fentanyl Citrate	Death
1330	UNK	Male	Unknown	25JUN2014	Death	Unknown	Unknown	None reported	None reported	Death
1331	61	Male	Unknown	25JUN2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1333	51	Female	Unknown	27JUN2014	Death	Unknown	Unknown	None reported	None reported	Death
1334	64	Female	Unknown	27JUN2014	Death	Unknown	Unknown	None reported	None reported	Death
1335	UNK	Male	Unknown	27JUN2014	Death	Unknown	Unknown	None reported	None reported	Death
1336	67	Male	Unknown	30JUN2014	Cardiac disorder	Unknown	Unknown	None reported	None reported	Death
1337	58	Female	Unknown	30JUN2014	Acute myeloid leukaemia, Hospitalisation, Myelodysplastic syndrome	Breakthrough cancer pain	Unknown	None reported	None reported	Death
1338	51	Female	01AUG2012	30JUN2014	Colon cancer recurrent	Breakthrough cancer pain	Unknown	Fentanyl, Roxanol, Ativan, Lovenox, Potassium	None reported	Death
1339	56	Male	Unknown	30JUN2014	Death	Unknown	Unknown	None reported	None reported	Death
1340	UNK	Female	Unknown	30JUN2014	Death	Breast cancer	2013-06-25 - UNK	Hydromorphone, Methadone	None reported	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1341	UNK	Male	Unknown	30JUN2014	Neoplasm progression	Unknown	2014-02-26 - UNK	None reported	None reported	Death
1342	UNK	Female	Unknown	30JUN2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1343	64	Female	Unknown	01JUL2014	Pancreatic carcinoma metastatic	Unknown	2 Years	None reported	None reported	Death
1344	88	Female	Unknown	01JUL2014	Death	Unknown	Unknown	None reported	None reported	Death
1345	UNK	Female	Unknown	01JUL2014	Neoplasm progression	Breakthrough cancer pain	2013-10-01 - UNK	None reported	None reported	Death
1346	27	Male	Unknown	03JUL2014	Complications of transplant surgery	Unknown	Unknown	None reported	None reported	Death
1347	55	Male	Unknown	03JUL2014	Metastasis, Small cell lung cancer	Unknown	Unknown	None reported	None reported	Death
1348	UNK	Male	Unknown	03JUL2014	Death	Unknown	2013-10-01 - UNK	None reported	None reported	Death
1349	UNK	Female	Unknown	07JUL2014	Rectal cancer metastatic	Unknown	Unknown	None reported	None reported	Death
1351	63	Female	01DEC2011, 13JUL2009	08JUL2014	Pain, Renal cell carcinoma	Pain control	Unknown	None reported	None reported	Death
1352	UNK	Male	Unknown	08JUL2014	Death	Unknown	Unknown	None reported	None reported	Death
1353	UNK	Male	Unknown	08JUL2014	Death	Unknown	Unknown	None reported	None reported	Death
1354	62	Male	Unknown	09JUL2014	Death	Unknown	Unknown	None reported	None reported	Death
1355	60	Female	05JUL2014	11JUL2014	Death	Unknown	Unknown	None reported	None reported	Death
1356	UNK	Female	Unknown	11JUL2014	Neoplasm progression	Unknown	2013-04-23 - UNK	None reported	None reported	Death
1357	UNK	Female	Unknown	11JUL2014	Neoplasm progression	Unknown	2013-04-23 - UNK	None reported	None reported	Death
1358	43	Male	Unknown	14JUL2014	Pancreatic carcinoma metastatic	Unknown	Unknown	None reported	None reported	Death
1359	55	Male	Unknown	14JUL2014	Pancreatic carcinoma metastatic	Unknown	Unknown	None reported	None reported	Death
1361	65	Female	Unknown	14JUL2014	Death	Unknown	Unknown	None reported	None reported	Death
1362	58	Female	Unknown	15JUL2014	Death	Liver metastasis,portal lymphadenopathy	Unknown	Oxycodone, Duragesic	None reported	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1363	75	Male	15SEP2013	15JUL2014	Death	Unknown	2013-04-23 - UNK	None reported	None reported	Death
1364	UNK	Male	Unknown	16JUL2014	Death	Unknown	Unknown	None reported	None reported	Death
1365	73	Male	Unknown	21JUL2014	Death	Unknown	Unknown	None reported	None reported	Death
1366	UNK	Male	Unknown	21JUL2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1367	73	Female	Unknown	22JUL2014	Death	Unknown	Unknown	None reported	None reported	Death
1368	68	Female	Unknown	22JUL2014	Death	Unknown	Unknown	None reported	None reported	Death
1369	UNK	Male	Unknown	22JUL2014	Death	Unknown	2014-06 - UNK	None reported	None reported	Death
1370	UNK	Male	Unknown	22JUL2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1372	61	Female	Unknown	23JUL2014	Breast cancer metastatic	Unknown	Unknown	None reported	None reported	Death
1373	UNK	Male	Unknown	25JUL2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1374	UNK	Unknown	01AUG2012	28JUL2014	Death	Unknown	Unknown	None reported	None reported	Death
1375	71	Male	27JUN2014	28JUL2014	Sepsis/Total organ failure	Chronic neuropathic pain	6/27/14 (1 day)	None reported	None reported	Death
1376	UNK	Female	Unknown	28JUL2014	Death	Unknown	Unknown	None reported	None reported	Death
1377	55	Female	Unknown	29JUL2014	Breast cancer metastatic	Unknown	Unknown	None reported	None reported	Death
1378	66	Female	Unknown	29JUL2014	Death	Unknown	Unknown	None reported	None reported	Death
1379	UNK	Female	Unknown	30JUL2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1380	73	Female	12JAN2013	31JUL2014	Death	Unknown	2014-04-21 - UNK	None reported	None reported	Death
1381	UNK	Male	Unknown	31JUL2014	Death	Unknown	2014-04-21 - UNK	None reported	None reported	Death
1382	UNK	Female	Unknown	31JUL2014	Death	Unknown	Unknown	None reported	None reported	Death
1383	86	Male	Unknown	04AUG2014	Cardiac disorder, Coronary artery bypass, Death, Myocardial infarction, Off label use, Prostate cancer	Lumbar pain	Unknown	Lidoderm Patch, Ms Contin, Sancuso, Voltaren Gel	None reported	Death
1384	UNK	Male	Unknown	04AUG2014	Death	Breakthrough pain	2012-08-11 - UNK	None reported	None reported	Death
1385	71	Female	Unknown	05AUG2014	Disease progression	Unknown	Unknown	None reported	None reported	Death
1386	50	Female	Unknown	05AUG2014	Metastatic neoplasm	Unknown	Unknown	None reported	None reported	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1387	46	Female	Unknown	05AUG2014	Death	Unknown	Unknown	None reported	None reported	Death
1389	UNK	Female	Unknown	06AUG2014	Death	Unknown	Unknown	None reported	None reported	Death
1390	UNK	Male	Unknown	07AUG2014	Neoplasm malignant	Unknown	Unknown	None reported	None reported	Death
1391	72	Male	26JUN2013	11AUG2014	Death	Unknown	Unknown	None reported	None reported	Death
1392	UNK	Male	Unknown	11AUG2014	Death	Unknown	Unknown	None reported	None reported	Death
1393	UNK	Male	Unknown	11AUG2014	Death	Unknown	Unknown	None reported	None reported	Death
1394	59	Male	Unknown	12AUG2014	Gastrointestinal carcinoma, Liver disorder	Cancer pain	Unknown	Duragesic, Ativan, Zofran, Fentanyl	None reported	Death
1395	71	Female	Unknown	12AUG2014	Death	Unknown	Unknown	None reported	None reported	Death
1396	76	Female	Unknown	12AUG2014	Lung neoplasm malignant	Cancer pain	Unknown	None reported	None reported	Death
1397	UNK	Female	Unknown	14AUG2014	Death	Unknown	Unknown	None reported	None reported	Death
1398	45	Female	Unknown	14AUG2014	Death	Unknown	Unknown	None reported	None reported	Death
1399	UNK	Female	Unknown	14AUG2014	Death	Unknown	Unknown	None reported	None reported	Death
1400	UNK	Female	Unknown	14AUG2014	Death	Unknown	Unknown	None reported	None reported	Death
1401	50	Female	23NOV2013	14AUG2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1402	UNK	Male	Unknown	15AUG2014	Death	Unknown	Unknown	None reported	None reported	Death
1403	54	Female	27NOV2013	15AUG2014	Breast Cancer, Death	Cancer pain	Unknown	None reported	Fentanyl Citrate	Death
1404	42	Male	30DEC2013	19AUG2014	Death	Unknown	Unknown	None reported	None reported	Death
1405	UNK	Female	Unknown	19AUG2014	Death	Unknown	2 Years	None reported	None reported	Death
1406	56	Female	01OCT2012	19AUG2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1407	UNK	Male	Unknown	20AUG2014	Death	Unknown	Unknown	None reported	None reported	Death
1408	29	Male	14DEC2012	20AUG2014	Testis cancer	Cancer pain	Unknown	None reported	None reported	Death
1409	40	Female	Unknown	21AUG2014	Death	Unknown	Unknown	None reported	None reported	Death
1410	73	Female	31OCT2012	21AUG2014	Death	Unknown	Unknown	None reported	None reported	Death
1411	UNK	Female	Unknown	21AUG2014	Breast cancer metastatic	Unknown	Unknown	None reported	None reported	Death
1412	68	Male	Unknown	22AUG2014	Renal cancer metastatic	Unknown	Unknown	None reported	None reported	Death
1413	UNK	Male	Unknown	22AUG2014	Completed suicide, Pain	Unknown	Unknown	None reported	None reported	Death
1414	UNK	Female	Unknown	25AUG2014	Sarcoma metastatic	Unknown	Unknown	None reported	None reported	Death

UBC ID	Patient		Date		Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
	Age	Gender	Event	Report						
1415	UNK	Female	Unknown	25AUG2014	Death	Unknown	Unknown	None reported	None reported	Death
1416	UNK	Female	Unknown	25AUG2014	Death	Unknown	Unknown	None reported	Fentanyl Citrate	Death
1417	49	Female	Unknown	27AUG2014	Death	Unknown	Unknown	None reported	None reported	Death
1418	UNK	Male	Unknown	27AUG2014	Death	Unknown	2014-06 - UNK	None reported	None reported	Death

[a] The source data for this patient did not include an event outcome of death. Death is noted in the preferred term for this case.

[b] Patient 1175 is also described in the table for pediatric exposures (Table 28).

There were two pediatric cases reported during this reporting period (Table 28). One case had an outcome of death and one case had an outcome of unknown at the time of this report.

There was a report of an 8 month old who was exposed to fentanyl and died. The reporter, an attorney, reported the death was related to the fentanyl use; however, this was not medically confirmed at the time of this assessment report.

The second pediatric case, with an outcome of unknown, was a 12-year-old female who was prescribed oral transmucosal fentanyl citrate for an unknown indication. The preferred term for this case was drug administered to patient of inappropriate age. No further details were obtained despite extensive follow-up attempts.

Table 28 Cases of Pediatric Exposures Received from TRIG Sponsors during the Reporting Period: 29 October 2013 - 28 August 2014

	Patient		Date							
UBC ID	Age	Gender	Event	Report	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome
1175[a]	0.7	Unknown	Unknown	24MAR2014	Death, Off label use	Unknown	Unknown	None reported	None reported	Death
1181	12	Female	Unknown	26MAR2014	Drug Administered To Patient Of Inappropriate Age	Unknown	Unknown	None reported	Fentanyl Citrate	Unknown

[a] Patient 1175 is also described in the table for cases of death (Table 27).

7.4 TIRF Product Surveillance Data [Metric 31]

7.4.1 Background

Surveillance data focusing on events of abuse, misuse, and death were evaluated using data from the RADARS® System for the time period 3rd quarter 2012 through 2nd quarter 2014. Data from five programs that gather data from unique populations along the spectrum of drug abuse were used to monitor for the non-medical use (abuse and misuse) of TIRF products. Drug diversion data are sparse for TIRF products and are therefore not included in this report. The data sources and the specific events evaluated in each are shown in Table 29 below.

Table 29 RADARS® System: Data Sources and Specific Events

Data Source	Abuse	Intentional Misuse	Unintentional Therapeutic Errors	Unintended General Exposures	Emergency Department Visits & Hospitalizations	Deaths	Major Medical Outcomes and Deaths[e]
1. Poison Center	✔ [a]	✔	✔	✔	✔	✔	✔
Treatment Center Surveys							
2. Opioid Treatment Programs	✔ [b]						
3. Key Informants Survey	✔ [b]						
4.. College Survey	✔ [c]						
5. Impaired Healthcare Workers Program	✔ [d]						

[a] Abuse defined as exposure resulting from intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high euphoric effect or some other psychotropic effect

[b] Abuse defined as a respondent endorsing the use of a product to get high in the past 30 days

[c] Abuse defined as endorsement of a non-medical use of a drug in the past 90 days

[d] All reported cases are considered abuse

[e] This column includes the events included in the column titled "deaths" as well as major medical outcomes that did not lead to death

Trends over time for the TIRF products were compared to three comparator groups that are not directly impacted by the TIRF REMS to determine how the trend in TIRF rates compares to the secular trend in other opioids. The comparators used in this report were:

- Schedule II IR opioids
- Schedule II opioids
- Schedule II opioids excluding methadone

The schedule II opioids comparator group was updated for this report to include sufentanil as it was recently released on the market. Additionally, schedule II opioids were analyzed with and without methadone as methadone prescriptions exclude dispensing in opioid treatment centers and therefore prescriptions are undercounted.

Data from IMS Health are used to estimate total prescriptions dispensed and total dosing units dispensed at the 3-digit ZIP-code level for all TIRF REMS opioids and comparator groups. Totals of prescriptions and dosing units in the three digit zip codes covered by the RADARS® System Programs were computed and used as the denominators when calculating product availability rates. IMS data does not capture methadone dispensed through opioid treatment programs, thus the count of methadone prescriptions is an undercount.

Rates of abuse, misuse, overdose, addiction and death were calculated using the 2010 US decennial census estimated from the three-digit zip codes covered in the RADARS® System Programs as the denominator.

Additional details can be found in the RADARS® System Report Protocol (Appendix 12.3).

7.4.2 Poison Center Program

The RADARS® System Poison Center Program obtains data from individuals within the general population and from healthcare providers who are seeking advice regarding potential toxic exposures, including exposures to prescription opioids and stimulants. The objectives of the Poison Center Program are to detect product-specific prescription drug abuse and misuse in near real-time and to identify geographic sites with disproportionately high rates of abuse and misuse. Poison center data collected through the System provide an estimate of change in intentional abuse for these drugs. The Poison Center Program gathers data from 48 regional US Poison Centers covering 46 states, including urban, suburban and rural regions (over 90% of the US population). In total, poison centers receive over 2.3 million exposure calls per year. Investigators at each participating poison center collect data using a nationally standardized electronic health record. The Poison Center Program provides heightened sensitivity and quick response time, which may help detect emerging prescription drug abuse and misuse problems.

7.4.3 Treatment Center (TC) Program

The Treatment Center Programs are comprised of both the Opioid Treatment Program (OTP) and the Survey of Key Informants' Patients (SKIP) Program. Data for this reporting period (collected in 2nd quarter 2014) from the OTP involved 61 methadone maintenance treatment programs in 34 states. The objectives of the OTP are to estimate 1-month prevalence and the injection rate of prescription and illicit opioid and non-opioid drugs among patients admitted to opioid treatment programs. In addition, the OTP seeks to determine the patient's drug of choice and the source of the primary drug. Patients enrolling in the participating OTPs are voluntarily recruited for the study and complete a self-administered anonymous questionnaire within the first week of admission. OTPs in rural and urban areas of the United States have been recruited as study sites.

Data collected in this reporting period (2nd quarter 2014) from the SKIP involved 106 substance abuse treatment programs covering 46 states. These primarily private treatment centers include representation from urban, suburban and rural centers. Each newly admitted patient with a diagnosis of prescription opioid analgesic abuse or dependence is offered the opportunity to complete a standardized self-administered questionnaire that solicits information on specific

prescription drugs abused in the past 30 days. The objectives of SKIP are to monitor the incidence of abuse/misuse of many different prescribed opioids, to determine the characteristics of the abuse/misuse patterns, and to develop intervention strategies.

The OTP and SKIP programs complement each other by addressing different socioeconomic demographics involved in prescription drug abuse. Both programs use a common base questionnaire so that data can be combined.

7.4.4 College Survey Program

The College Survey program is an online questionnaire that collects data from self-identified students attending a 2- or 4-year college, university or technical school at least part-time during the specified sampling period. Data on non-medical use (abuse/misuse) of specific prescription drugs are collected at the completion of the fall and spring academic semesters/quarters and at the end of the summer. The objectives of the College Survey Program are to estimate the scope of non-medical prescription drug use among US college students, determine the drug source and determine the route of drug administration among these students. A target of 2000 surveys is completed three times per year with enrollment stratified into the four US Census-regions to ensure nationwide distribution of respondents. A nationwide panel company is utilized to identify and target ideal responders. Students are sent an invitation to participate in the study and they receive credits upon completion of the survey. The survey inquires about the nonmedical use of prescription drugs by capturing product specific endorsements.

7.4.5 Impaired Healthcare Workers Program

The Impaired Health Care Worker Program is a subset of three contributing programs. Data on impaired healthcare works are aggregated by combining data from these three sources into one data set:

- Reports from several regulatory agencies, including medical boards, pharmacy boards, dental boards and nursing boards are obtained and summarized. These agencies specialize in the detection, treatment and sanctioning of impaired health workers who are involved in the diversion of prescription pharmaceuticals.
- Poison Center case notes are reviewed and cases which indicate the individual involved in the exposure is a health care worker are flagged.
- Respondents in the Treatment Center Programs self-identify as health care workers on the questionnaire.

7.4.6 Results

Summary results of the analyses of the four data sources are presented below. The full report from the RADARS® System Program is included as Appendix 12.2.

7.4.7 Population Rates

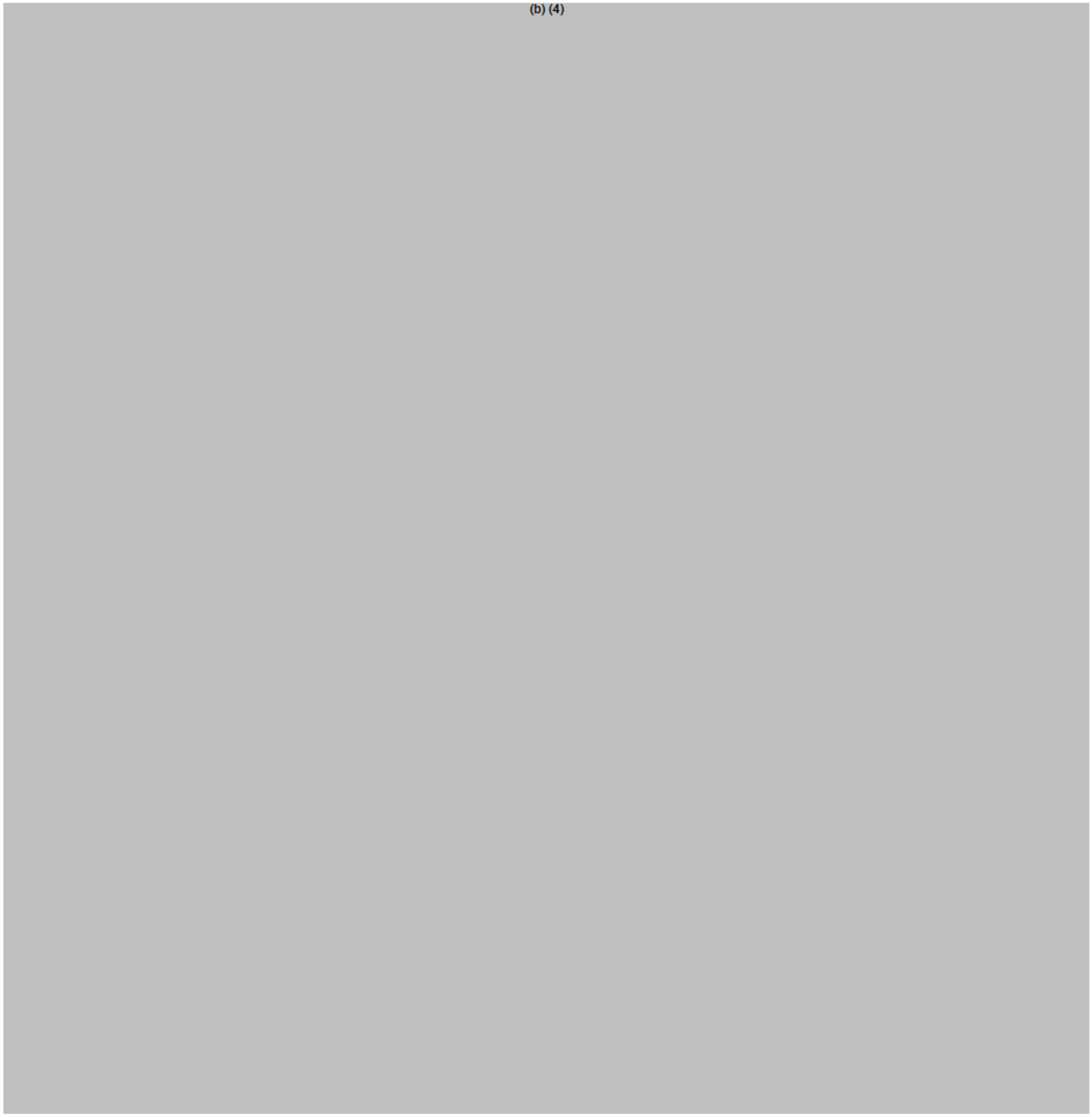
(b) (4)

(b) (4)

7.4.8 Prescription Rates

(b) (4)

(b) (4)



7.4.9 Pediatric Exposures

(b) (4)

(b) (4)

7.4.10 Comparison of Cases from Reporting Period 1 to Reporting Period 2

(b) (4)

8 PERIODIC SURVEYS OF STAKEHOLDERS

Surveys were conducted to assess patients'/caregivers', pharmacists', and prescribers' KAB regarding the safe use of TIRF medicines as described in the educational materials for all stakeholders, enrollment form (pharmacists and prescribers only), Full Prescribing Information (pharmacists and prescribers only) and medication guides (prescribers and patients) for each product, and the PPAF (prescribers and patients only). The survey protocols describe the administration of the individual surveys that were conducted among patients who are treated with TIRF medicines or their caregivers, prescribers, and pharmacists; the survey KAB reports include summarization of all data collected during the survey (see Appendix 12.4.1, 12.4.2, and 12.4.3, respectively, for the patient, pharmacist, and prescriber KAB reports which include the protocol and survey). Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

8.1 Key Risk Messages

The questions and statements within the KAB surveys for patients/caregivers, pharmacists, and prescribers were constructed to test the stakeholders' understanding of the key risk messages of the REMS. The TRIG established a desired threshold of 65%. A correct response rate of 65% or greater was considered to represent adequate understanding of each concept or key risk message. The purpose of this threshold was to assist TRIG in tracking and monitoring the data for each key risk message across each wave ultimately providing direction in determining which area(s)

would require improvement to ensure the patient/caregiver, pharmacist, and prescriber KAB surveys were meeting the goals of the REMS.

8.2 Patient KAB Survey

8.2.1 Background and Survey Statistics

The specific goals of the TIRF medicines patient/caregiver KAB survey were to evaluate the level of knowledge and assess the attitudes and behavior of patients/caregivers regarding TIRF medicines. The focus of the survey included the potential for life-threatening breathing problems that can lead to death, the need for patients to take TIRF medicines if they are opioid-tolerant and strictly follow the directions of the HCP, the caution that patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to an HCP, the requirements that patients should not give TIRF medicines to anyone else even if they have the same symptoms, and that TIRF medicines should be stored in a safe place away from children and properly disposed of. The survey also included questions about whether patients received, read, and understood the product-specific Medication Guide and the PPAF.

For the patient KAB survey, invitations (and reminders) were sent to all known patients/caregivers who had filled a prescription within the 4 months prior to survey launch. From among those who responded to the invitation, 229 patients/caregivers completed the survey (there were only 4 caregivers who participated in the survey). Although the survey had a target of 300 completed responders, the pool of 1343 patients/caregivers who were mailed the invitation was small. The response of 229 completed surveys from this limited pool is within the expected response rate to mailed invitations (17.1%; 229/1343).The target 300 eligible completed surveys was not achieved, a sample of 229 completed surveys is adequate to draw conclusions regarding patient understanding of safe use of TIRF medicines.

8.2.2 Patient Survey Results

In this 36-month survey, all but one of the questions included as part of the key risk messages had a correct response rate of >69%. There was only one question within a key risk message (Question 12 in Key Risk Message 3) that had a component with an understanding rate below the desired threshold of 65% (Component 12b*: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine;* correct response *'True';* correct response rate 36.7%). This concept also scored low for prescribers (61.0%) for this reporting period.

In addition, there was one question included as part of the additional questions about the safe use of TIRF medicines and not included as a key risk message (Question 10; *For which of the following conditions should you use a TIRF medicine?*) that had a component with an understanding rate below the desired threshold of 65% (Component 10e; *Long-lasting painful conditions not caused by cancer*; correct response '*No*', correct response rate 25.3%). This component also had a low correct response rate in the previous survey waves. Although the questions are worded differently for the 36-month survey period, this concept also scored low for pharmacists (43.7%). These components were the only low scoring components in all three waves of the patient/caregiver KAB survey.

Question 32 (*Did the doctor or someone in the doctor's office explain the Patient-Prescriber Agreement Form to you?*) shows an increased response (77.7%) compared to the previous two waves which supports that the healthcare professionals are discussing with their patients the safe use and risks of TIRF medicines.

The consistently high level of patient understanding of key risk messages in the 24-month and 36-month surveys indicates that the REMS goals are being met with the tools currently in place. The higher level of understanding in patients who read most or all of the medication guide demonstrates effective communication of the key risk messages, which may also be reinforced by prescribers and pharmacists. For complete data and results see Appendix 12.4.1.

8.3 Pharmacy KAB Survey

8.3.1 Background and Survey Statistics

The specific goals of the TIRF medicines pharmacist KAB survey were to assess pharmacist understanding of the risks associated with TIRF medicine use, the specific indications for treatment with TIRF medicines, and that TIRF medicines are contraindicated in opioid non-tolerant patients. The survey also included questions about the pharmacists' access to educational materials for TIRF medicines.

For the pharmacist KAB survey, invitations (and reminders) were sent to a random sample of pharmacies enrolled in the TIRF REMS Access Program. From among those who responded to the invitation, 300 pharmacists completed the survey; thus the program goal was achieved within the specific time period.

8.3.2 Pharmacy Survey Results

In this 36-month survey, all but one of the questions/components included as part of the key risk messages had a correct response rate of >70%. There was only one question within a key risk message (Question 9 [*Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients?*] in Key Risk Message 2) that had a component with an understanding rate below the desired threshold of 65% (Component 9e: *Chronic non-cancer pain*; correct response "*No*"; correct response rate 43.7%). This component also had a low correct response rate in the previous survey waves. For the other 4 components of Question 9, the desired responses were greater than 86% in the 36-month survey. It should be noted that pharmacist knowledge of uses for which TIRF medicines are not indicated is not a goal of the TIRF REMS. This concept also scored low patients/caregivers (25.3%; presented as *Long-lasting painful conditions not caused by cancer*).

In addition, there were two questions included as part of the additional questions about the safe use of TIRF medicines (and not included as part of a key risk message) that had a component with an understanding rate below 65%. The correct response rate for Component 6a which addresses knowledge that a cancer patient should not be started on a TIRF medicine and an around-the-clock opioid at the same time was 63.3%. This concept also scored low for prescribers (60.0%) during this reporting period. The correct response for component 11f that addresses the knowledge that patients are considered opioid-tolerant if taking an equianalgesic dose of another oral opioid one week or longer was 59.0%. These concepts also scored low for prescribers (59.0%) during this reporting period.

The consistently high level of pharmacist understanding of key risk messages in the 24-month and 36-month surveys indicates that the Education Program for Prescribers and Pharmacists is meeting the goals of the TIRF REMS. Changes will be implemented into the 48-month Pharmacist KAB survey based on FDA feedback received on the 24-month assessment report. For complete data and results see Appendix 12.4.2.

8.4 Prescriber KAB Survey

8.4.1 Background and Survey Statistics

The specific goals of the TIRF medicines prescriber KAB survey were to assess prescribers' understanding of the risks associated with TIRF medicine use, the selection of appropriate patients for treatment with TIRF medicines, preventing inappropriate conversion between TIRF medicines, and ensuring safe use of TIRF medicines while preventing exposure to children and others for whom TIRF medicines were not prescribed.

For the prescriber KAB survey invitations (and reminders) were sent to a random sample of prescribers enrolled in the TIRF REMS Access Program. From among those who responded to the invitation, 300 prescribers completed the survey; thus, the program goal was achieved within the specific period.

8.4.2 Prescriber Survey Results

In the 36-month prescriber KAB survey, of the 21 components of the 4 key risk messages, only 1 component had a response rate less than the desired threshold of 65%. As a measure of prescribers' behavior, 62.0% (n=186) of respondents gave the desired response "No" to Question 9 (*In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Component 9e: Chronic non-cancer pain*). The response from prescribers regarding the desired response that TIRF medicines are not prescribed for non-cancer pain has been consistently low for all 3 surveys (Wave 1: 54.3%; Wave 2: 58.9%; Wave 3: 62.0%). Based on FDA feedback an additional question will be added to the 48-month survey asking prescribers why they feel this is an appropriate use of a TIRF medicine. For the other 4 components of Question 9, the desired responses were greater than 87% in the 36-month survey.

In addition, there were four questions included as part of the additional questions about the safe use of TIRF medicines (and not included as part of a key risk message) that had a component with an understanding rate below the desired threshold of 65%. The correct response rate for component 6a which addresses knowledge that a cancer patient should not be started on a TIRF medicine and an around-the-clock opioid at the same time was 63.3%. This concept also scored low for pharmacists. The desired response of '*False*" for component 18c (*Instruct patients that, if they stop taking their around -the-clock opioid medicine, they can continue to take their TIRF medicine*) that assessed prescriber behavior was selected by 61.0% of prescribers. This concept also scored low in the patient/caregiver KAB survey for this reporting period. Similarly, Question 19, which addresses the knowledge that patients should not continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine had a correct response rate of 59.7%. This concept also scored low in the patients/caregiver KAB survey for this reporting period. In response to Question 11 component 11f, that addresses the knowledge that patients are considered opioid-tolerant if taking an equianalgesic dose of another oral opioid one week or

longer, was selected by 59.0% (177) of prescribers. For this reporting period, pharmacists also had a similar low rate of correct response for this concept (59.0%).

The consistently high level of prescriber understanding of key risk messages in the 24-month and 36-month surveys indicates that the Education Program for Prescribers and Pharmacists is meeting the goals of the TIRF REMS. Changes will be implemented into the 48-month Prescriber KAB survey based on FDA feedback received on the 24-month TIRF REMS assessment report. For complete data and results see Appendix 12.4.3.

8.5 Overall Conclusion for KAB Results:

The TRIG will evaluate the concepts that have scored low among stakeholders to determine if any action is warranted. The TRIG will continue to work with the FDA to refine, on a continual basis, the steps to mitigate risks associated with TIRF medicines.

9 FDA COMMUNICATIONS

During this reporting period REMS Modification 2 was approved and implemented. Modification 2 for the TIRF REMS consisted of the following:

- Incorporate closed system pharmacies into the TIRF REMS Access Program
- Correct minor inconsistencies between the FDA provided versions and the current PDF versions of REMS materials

Submission of REMS Modification 3 was completed on 10 December 2014. Modification 3 for the TIRF REMS consisted of the following:

- Updated REMS materials to eliminate product specific information which does not impact the safe use of TIRF products
- Updated REMS materials to reference the TIRF Products webpage on the TIRF REMS Access website
- Updated REMS materials to remove reference to deactivating patients shown to have multiple prescribers in an overlapping timeframe
- Incorporated revised assessment metrics into the Supporting Document
- Revised Education Program to emphasize and strengthen appropriate conversion and patient counseling information
- Updated REMS and Supporting Document to clarify deactivation of a patient PPAF as opposed to the patient record
- Updated pharmacy overview documents and FAQ to call out cash claim requirement
- Updated TIRF REMS Access website to incorporate items above and link respective Full Prescribing Information and Medication Guides to DailyMed
- Updated Education Program and Knowledge Assessment to incorporate approved labeling supplement

TRIG is currently awaiting feedback from FDA on REMS Modification 3 which includes the revised Assessment Plan aligning to the Agency's 21 August 2014 *REMS Acknowledgement/ REMS Assessment Plan Revision* communication to the TRIG and individual TIRF products application holders. Although Modification 3 is not approved, this assessment report has addressed the metrics aligning with the revised assessment plan provided in the *REMS Assessment Acknowledgement/REMS Assessment Plan Revision* and presented in Modification 3.

10 POST-APPROVAL STUDIES AND CLINICAL TRIALS

FDA should refer to the most recent periodic safety report from each TIRF sponsor for updated information on post-approval studies and/or clinical trials.

11 OVERALL CONCLUSIONS

The TIRF REMS Access Program was approved on 28 December 2011 and successfully launched on 12 March 2012, approximately 11 weeks after approval. This 36-month assessment report covers the timeframe between 29 October 2013 and 28 October 2014.

A major focus during this reporting period was re-enrollment of all stakeholders in the program. As part of re-enrollment, stakeholders were re-educated in order to ensure understanding about the safe use and risks of TIRF medicines. Extensive efforts are made using multiple modalities to reach all stakeholders whose enrollment status or PPAF is nearing expiration. Re-enrollment activities continue ensuring appropriate access to TIRF medicines.

REMS enrollment continues to increase, with 2,027 new prescribers, 1,585 new pharmacies, and 1 new distributor enrolled in this reporting period. A total of 159,560 prescriptions were presented for dispensing during this reporting period, and 145,084 (90.9%) prescriptions did not encounter any REMS-related rejection prior to being authorized. These data indicate that the program does not present a significant barrier to accessing these important medications while continuing to meet the safety goals of the REMS.

The number of prescriptions dispensed outside the established PPAF requirements was nearly eliminated as a result of the corrective actions implemented during this reporting period to significantly reduce this occurrence.

The TIRF REMS Access Program continues to monitor the electronic systems and stakeholder reports for issues and, where appropriate, corrective actions or system improvements are instituted.

During the current reporting period, 145 instances of stakeholder non-compliance with the TIRF REMS Access program were reviewed and investigated. This included 120 prescriber reports, 1 wholesaler/distributor report, 17 non-closed system pharmacy reports and 7 closed system pharmacy reports. Five of these closed system pharmacy non-compliance reports were identified during the audits of the 7 enrolled closed system pharmacy entities. Each affected entity was issued a notice through the NCRT and as a result all investigations have been closed.

As per the TRIG's agreement with FDA, inpatient pharmacy hospital audits have not yet been conducted. The TRIG is developing a process to accomplish inpatient pharmacy audits. Therefore, inpatient pharmacy audit data will be included in the 48-month assessment report.

The REMS goal of educating prescribers and pharmacists on the potential for misuse, abuse, addiction, and overdose is being documented through the completion of the Knowledge Assessment, which is required for enrollment. Effectiveness of the educational program is evaluated through the pharmacy and prescriber KAB surveys that are performed prior to each assessment report. Results of the 36-month surveys indicate a high level of understanding of safe use of TIRF medicines by pharmacists and prescribers. Key risk messages that are important for these stakeholders to understand include the fact that TIRF medicines are contraindicated in opioid non-tolerant patients, are only indicated for the management of breakthrough pain in adult cancer patients, contain fentanyl with abuse liability similar to other opioid analgesics, and are not interchangeable with each other on a mcg-to-mcg basis regardless of route of administration. Due to the high level of understanding of these concepts by pharmacists and prescribers, no modifications to the educational program or Knowledge Assessment are recommended at this time.

Patient education is completed through HCP counseling and completion of a PPAF. The patient KAB survey results indicate that the patient-oriented educational materials including the PPAF and Medication Guide for each product are effective tools at communicating safe use messages to patients, including the importance of not sharing TIRF medicines, taking TIRF medicines as prescribed, and properly disposing unused TIRF medicines. One identified area of potential improvement is patient understanding of the need to stop taking TIRF medicines if around-the-clock opioid therapy is stopped. The proposed Modification 3 includes updates to the education program to reinforce the importance of this information being shared with patients by pharmacists and prescribers.

Data collected through the RADARS® System showed that there were few event counts for TIRF products for all the Poison Center outcome variables: intentional abuse, intentional misuse, unintentional therapeutic errors, unintentional general exposures, emergency room visits or hospitalizations and major outcomes or death. Population rates for the Poison Center, Treatment Center and College Survey outcome variables tended to be lower than rates for Schedule II IR opioids, Schedule II opioids and Schedule II opioids excluding methadone. Prescription rates for the TIRF REMS products and Poison Center outcomes differed only occasionally from the comparator opioid groups. However, in the Treatment Center and College Survey, populations that are likely to have more experienced users, prescription rates for TIRF products tended to be higher than those for comparator opioids.

The analysis of spontaneous reports of adverse events of interest aggregated data from TRIG sponsors with currently marketed products. There were 367 unique case reports that met the specified criteria for addiction, overdose, death, and pediatric exposures. After a review of the associated MedWatch Forms or narratives for root cause analysis, no reports of inappropriate conversions between TIRF products were noted. Additionally, none of the narratives indicated accidental, unintentional exposures or use by non-opioid tolerant patients. There were only two cases of pediatric exposure; neither provided sufficient detail to perform a root cause analysis.

Data from the safety surveillance of adverse events of interest as well as RADARS® System data are consistent in showing low numbers of abuse, overdose and pediatric exposures cases associated with TIRF medicines. The primary RADARS® System data sources, with the exception of Poison Center data, are solicited via survey (Treatment Programs and College

Surveys) and describe patterns of abuse or misuse. Trends comparing RADARS® System data with the 3 selected comparator groups showed no substantial differences; solicited reports from the two survey populations were somewhat higher than the comparator groups, but showed a decline in rates over the time period.

Poison Control and adverse event reports from sponsors are spontaneously reported. The Poison Center data show a small number of reported deaths, whereas 98.6% of the spontaneous reports with the specified adverse events of interest had an outcome of death. In the case of Poison Center data, cases are generally identified in the course of the reporter asking for assistance regarding an exposure; an outcome of death may be obtained during follow-up by the Poison Center. The predominance of death reports in the data provided by the TIRF medicines manufacturers was not unexpected, given that patients who are treated with TIRF medicines for the labeled indication are generally very ill from their underlying condition. There were few deaths with events describing outcomes specifically associated with respiratory or cardiac failure.

Based on the data provided in this TIRF REMS Access Program Assessment Report the TRIG concludes that the REMS is meeting its established goals. The consistent high level of knowledge demonstrated by pharmacists, prescribers and patients provides evidence that the current tools are effectively communicating the important safety messages to key stakeholders. Based on our analysis of the data for this 36-month assessment, the TRIG is recommending no further REMS modifications beyond Modification 3 which is pending approval at this time.

12 APPENDICES

12.1 Safety Surveillance Aggregate Line Listing Preferred Terms

12.2 RADARS® System Program Report

12.3 RADARS® System Program Report Protocol

12.4 Periodic Stakeholder Surveys

Case Criteria:

- Only US cases
- No AAPCC or literature search cases
- In addition to performing searches on the below preferred terms, sponsors will search for:
  - All cases with an outcome of death
  - Cases related to patients aged 0 through 18
- Cases to be included in the reporting period date range will be based on MedWatch Form field "Date Received by Manufacturer" (G4)

Preferred Terms for FDA Requested Cases of Addiction, Death, Overdose and Pediatric Exposure

Primary SOC	High Level Group	High Level Term	Preferred Term
Overdose			
Injury, poisoning and procedural complications	Medication errors	Overdoses	Accidental overdose
Injury, poisoning and procedural complications	Medication errors	Overdoses	Intentional overdose
Injury, poisoning and procedural complications	Medication errors	Overdoses	Overdose
Injury, poisoning and procedural complications	Medication errors	Overdoses	Prescribed overdose
Death			
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Accidental death
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Brain death
General Disorders and administration site conditions	Fatal outcomes	Death and sudden death	Cardiac death
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Death
General disorders and administrations site conditions	Fatal outcomes	Death and sudden death	Death neonatal
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Sudden cardiac death
General Disorders and administration site conditions	Fatal outcomes	Death and sudden death	Sudden death
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Agonal death struggle
General disorders and administration site conditions	General system disorders NEC	General signs and symptoms NEC	Apparent death
Cardiac disorders	Cardiac arrhythmias	Ventricular arrhythmias and cardiac arrest	Cardio-respiratory arrest
Cardiac disorders	Cardiac arrhythmias	Ventricular arrhythmias and cardiac arrest	Cardiac arrest
Respiratory, thoracic and mediastinal disorders	Respiratory disorders NEC	Breathing abnormalities	Respiratory arrest
Pregnancy, puerperium and perinatal conditions	Abortions and stillbirth	Stillbirth and foetal death	Foetal death
Misuse			
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Intentional drug misuse
Abuse			

Primary SOC	High Level Group	High Level Term	Preferred Term
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug abuse
Inappropriate			
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Drug administered at inappropriate site
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Inappropriate schedule of drug administration
Medication Error			
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Incorrect dosage administered
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Inappropriate schedule of drug administration
Accidental			
Injury, poisoning and procedural complications	Medication errors	Accidental exposures to product	Accidental exposure to product
Injury, poisoning and procedural complications	Medication errors	Accidental exposures to product	Accidental exposure to product by child
Injury, poisoning and procedural complications	Medication errors	Overdoses	Accidental overdose
Injury, poisoning and procedural complications	Chemical injury and poisoning	Poisoning and toxicity	Accidental poisoning
General disorders and administration site conditions	Product quality issues	Product packaging issue	Failure of child resistant mechanism for pharmaceutical product
Dependence			
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Dependence
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug dependence
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug dependence, antepartum
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug dependence, postpartum
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Polysubstance dependence

Text-String Search Terms for Narratives

Addiction	Multiple drug overdose	Son	Nephew
Overdose	Expired	Daughter	Aunt
Drug dependence	Passed away	Grandmother	Uncle
Death	Infant	Grandfather	Mom
Pediatric exposure	Child	Sister	Pop
Died	Mother	Brother	Dad
Fatal	Father	Niece	

RADARS® System Report

Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS): Surveillance Monitoring

For

Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)
Depomed, Inc.
Galena Biopharma, Inc.
Insys Therapeutics Inc.
Mallinckrodt Pharmaceuticals
Meda Pharmaceuticals, Inc.
Mylan, Inc.
Par Pharmaceutical, Inc.

December 16, 2014

Level One Care for ALL

Saving Lives with Answers

FOLLOWING THIS PAGE, FDA_1804 TO FDA_1896 WITHHELD IN FULL AS B(4)/CCI

Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS): Surveillance Monitoring Protocol

For

Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)
Depomed, Inc.
Galena Biopharma, Inc.
Insys Therapeutics Inc.
Mallinckrodt Pharmaceuticals
Meda Pharmaceuticals, Inc.
Mylan, Inc.
Par Pharmaceutical, Inc.

Dec 15, 2014

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7. Appendices

7.2 Shell Tables

Table x.x.x
The RADARS® System Poison Center Program
Intentional Abuse Rates over Time by Drug Group
Third Quarter 2012 through Third Quarter 2013

	Intercept				Slope			
Drug Group	Rate (95% CI)	p-value	Rate Ratio (95% CI)	p-value for difference	Percent Quarterly Change (95% CI)	p-value	% difference (95% CI)	p-value for difference
Population Adjusted Rate								
TIRF Products	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.
Schedule II IR Opioids	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Schedule II Opioids	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Schedule II Opioids Excluding Methadone	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Prescription Adjusted Rate								
TIRF Products	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.
Schedule II IR Opioids	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Schedule II Opioids	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Schedule II Opioids Excluding Methadone	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx

Table x.x.x
The RADARS® System Treatment Center Programs
Past 90 Day Endorsement of Non-Medical Use Over Time by Drug Group
Third Quarter 2012 through Third Quarter 2013

	Intercept				Slope			
Drug Group	Rate (95% CI)	p-value	Rate Ratio (95% CI)	p-value for difference	Percent Quarterly Change (95% CI)	p-value	% difference (95% CI)	p-value for difference
Population Adjusted Rate								
TIRF Products	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.
Schedule II IR Opioids	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Schedule II Opioids	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Schedule II Opioids Excluding Methadone	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Prescription Adjusted Rate								
TIRF Products	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.
Schedule II IR Opioids	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Schedule II Opioids	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Schedule II Opioids Excluding Methadone	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx

Table x.x.x
The RADARS® System College Survey Program
Past 90 Day Mentions Over Time by Drug Group
Third Quarter 2012 through Third Quarter 2013

	Intercept				Slope			
Drug Group	Rate (95% CI)	p-value	Rate Ratio (95% CI)	p-value for difference	Percent Quarterly Change (95% CI)	p-value	% difference (95% CI)	p-value for difference
Population Adjusted Rate								
TIRF Products	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.
Schedule II IR Opioids	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Schedule II Opioids	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Schedule II Opioids Excluding Methadone	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Prescription Adjusted Rate								
TIRF Products	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.
Schedule II IR Opioids	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Schedule II Opioids	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Schedule II Opioids Excluding Methadone	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx

Table x.x.x
The RADARS® System Impaired Healthcare Worker Program
Cases Over Time by Drug Group
Third Quarter 2012 through Third Quarter 2013

	Intercept				Slope			
Drug Group	Rate (95% CI)	p-value	Rate Ratio (95% CI)	p-value for difference	Percent Quarterly Change (95% CI)	p-value	% difference (95% CI)	p-value for difference
Population Adjusted Rate								
TIRF Products	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.
Schedule II IR Opioids	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Schedule II Opioids	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Schedule II Opioids Excluding Methadone	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Prescription Adjusted Rate								
TIRF Products	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.
Schedule II IR Opioids	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Schedule II Opioids	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx
Schedule II Opioids Excluding Methadone	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx

12.4.1 Patient KAB Survey

Title:	**Transmucosal Immediate Release Fentanyl (TIRF) REMS Assessment** **Quantitative Testing of Patient Knowledge, Attitudes, and Behavior (KAB) about TIRF Products' Safety and Use Information**
Document Number	Wave 3, 36-month REMS Assessment; Version 1.0
Survey Time Period	18 August 2014 to 22 October 2014
Product Name:	Transmucosal Immediate Release Fentanyl
Sponsor:	**TIRF REMS Industry Group (TRIG) of Companies:** Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc Galena Biopharma, Inc. Insys Therapeutics Mallinckrodt Pharmaceuticals Meda Pharmaceuticals Mylan, Inc. Par Pharmaceutical, Inc.
Date:	19 December 2014

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TABLE OF CONTENTS **PAGE**

TABLE OF CONTENTS 2
LIST OF TABLES 3
LIST OF APPENDICES 4
LIST OF ABBREVIATIONS 5
1. PATIENT SURVEY BACKGROUND 6
2. PATIENT SURVEY OBJECTIVES 7
3. SURVEY METHODOLOGY 7
3.1 Survey Sample 7
3.1.1 Eligibility 8
3.1.2 Recruitment 8
3.1.2.1 Direct Letter Program 8
3.2 Questions and Statements on Key Risk Messages 8
3.2.1 Key Risk Message 1 9
3.2.2 Key Risk Message 2 9
3.2.3 Key Risk Message 3 10
3.2.4 Key Risk Message 4 10
3.2.5 Key Risk Message 5 10
3.2.6 Key Risk Message 6 11
4. Statistical Methods 11
4.1 Study Population 11
4.1.1 Primary Analysis Population 11
4.1.2 Sub-groups of Interest 11
4.1.2.1 Primary Analyses 13
4.1.2.2 Secondary Analyses 13
4.1.3 Patient Report of an Adverse Event, Product Complaint, or Medical Information Request during the Survey 13
5. RESULTS 13
5.1 Survey Participants 13
5.1.1 Survey Participant Administration Results 13

5.1.2 Patient/Caregiver Demographics 19
5.1.3 TIRF Medicines Education Materials 22
5.1.4 Patient-Prescriber Agreement Form 27
5.2 KAB Survey Objectives 29
5.2.1 Key Risk Message Results 29
5.2.1.1 Key Risk Message 1 29
5.2.1.2 Key Risk Message 2 29
5.2.1.3 Key Risk Message 3 31
5.2.1.4 Key Risk Message 4 33
5.2.1.5 Key Risk Message 5 34
5.2.1.6 Key Risk Message 6 35
5.2.2 Other Survey Questions 38
5.2.2.1 Additional Questions about TIRF Medicines Safety 38
5.2.3 Sub-group Analysis of Responses to Key Risk Messages 40
5.2.3.1 Reading the Medication Guide (Sub-group S-1) 40
5.2.3.2 All other Sub-group Analyses 42
5.3 Spontaneous Reporting of Adverse Events, Product Complaints, or Medical Information Requests 43
5.4 Summary of Correct Responses for Key Risk Messages 43
6. FDA FEEDBACK 47
7. DISCUSSION, AND CONCLUSIONS 47

LIST OF TABLES

Table 1. Survey Participant Administration Results 15
Table 2. Survey Participant Screening Results 16
Table 3. Time to Complete Survey for Completers (Minutes) 19
Table 4. Demographic Characteristics of Eligible Patients/Caregivers 20
Table 5. Responses to Questions About TIRF Medication Guides 23
Table 6. Responses to Questions About the Patient-Prescriber Agreement Form 28

Table 7. Key Risk Message 1: TIRF Medicines Can Cause Life-Threatening Breathing Problems That Can Lead to Death 29
Table 8. Key Risk Message 2: Patients Should Not Take TIRF Medicines If They Are Not Opioid Tolerant..... 30
Table 9. Key Risk Message 3: TIRF Medicines Should Be Taken Exactly As Prescribed By The Healthcare Provider..... 32
Table 10. Risk Message 4: Patients Should Not Switch From a TIRF Medicine to Another Medicine That Contains Fentanyl Without Talking to a Healthcare Provider 34
Table 11. Key Risk Message 5: Patients Should Not Give TIRF Medicines to Anyone Else Even if They Have the Same Symptoms..... 35
Table 12. Key Risk Message 6: TIRF Medicines Should be Stored in a Safe Place Away From Children and Properly Disposed 36
Table 13. Responses to Additional Questions about the Safe Use of TIRF Medicines..... 38
Table 14. Correct Responses and Response Rates to Key Risk Message Questions Based on Extent of Reading of Medication Guide 41
Table 15. Summary of Correct Responses for Key Risk Messages..... 44
Table 16. Correct/Desired Response Rate of Low Scoring Questions across the Three Patient/Caregiver KAB Survey Waves..... 48

LIST OF APPENDICES

Appendix A Patient Survey Protocol..... 50
Appendix B Patient Survey Listings and Sub-group Analyses Tables 51
Appendix C Patient Survey Protocol Track Change Document: Comparison of 24-month Survey to 36-month Survey 52

LIST OF ABBREVIATIONS

AE/PC PSP	Adverse Event/Product Complaint Project Specific Procedure
CI	Confidence Interval
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HCP	Healthcare Professional
KAB	Knowledge, Attitudes and Behavior
NA	Not Applicable
PPAF	Patient-Prescriber Agreement Form
PBM	Pharmacy Benefits Manager
REMS	Risk Evaluation and Mitigation Strategy
SCC	Survey Coordinating Center
SD	Standard Deviation
TIRF	Transmucosal Immediate Release Fentanyl
TIRF Medicines	Transmucosal Immediate Release Fentanyl products
TIRF REMS Access Program	REMS Program for TIRF medicines
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States
USPS	United States Postal Service

1. PATIENT SURVEY BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines are a class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® [fentanyl citrate oral transmucosal lozenge] and equivalent generics) who are already receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The TIRF Risk Evaluation and Mitigation Strategy (REMS) Industry Group (TRIG) includes Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.), Depomed, Inc., Galena Biopharma, Inc., Insys Therapeutics, Mallinckrodt Pharmaceuticals, Meda Pharmaceuticals, Mylan, Inc., and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a shared system REMS is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on 28 December 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by the following:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

2. Preventing inappropriate conversion between TIRF medicines.

3. Preventing accidental exposure to children and others for whom it was not prescribed.

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess patients'/caregivers' knowledge, attitudes, and behavior (KAB) regarding the safe use of TIRF medicines as described in the educational materials. Administration of the surveys conducted among patients/caregivers who are enrolled in the TIRF REMS Access Program is described in the protocol (See Appendix A). Note: Protocol and Survey question revisions from the 24-month assessment report are identified in the track change version found in Appendix C.

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

This report describes the results from the patient surveys conducted for the 36-month TIRF REMS Access Program Assessment. The 36-month KAB survey launched on 18 August 2014 and closed on 22 October 2014.

2. PATIENT SURVEY OBJECTIVES

The evaluation survey uses a questionnaire to document the level of knowledge and assess the attitudes and behavior of patients regarding the following key information and risk messages communicated through the REMS:

1. TIRF medicines can cause life-threatening breathing problems that can lead to death.
2. Patients should not take TIRF medicines if they are not opioid tolerant.
3. TIRF medicines should be taken exactly as prescribed by the healthcare provider.
4. Patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.
5. Patients should not give TIRF medicines to anyone else even if they have the same symptoms.
6. TIRF medicines should be stored in a safe place away from children and properly disposed.

The survey also includes questions about whether patients received, read, and understood the product-specific Medication Guide and Patient-Prescriber Agreement Form (PPAF).

3. SURVEY METHODOLOGY

This section summarizes the survey design and the questions that were constructed to test patient understanding of the key risk messages of the REMS. Full details of the survey design are in the protocol, provided in Appendix A.

3.1 Survey Sample

This survey was conducted among patients who had a prescription filled for a TIRF medicine within the 120 days prior to the survey launch date. A sample of 300 patients treated with TIRF medicines was targeted for this third KAB survey conducted from 18 August 2014 to 22 October 2014. The size of the sample was determined on both practical and statistical considerations. The survey was written to reflect wording for both methods of survey administration: Internet-based and telephone.

3.1.1 Eligibility

Eligibility criteria included patients, 18 years of age or older, and caregivers, 18 years of age or older, who cared for patients who were unable to take the survey for themselves. Respondents who (or respondents whose immediate family members) had ever worked for any of the TRIG companies, McKesson Specialty Care Solutions, RelayHealth, United BioSource Corporation (UBC), or the FDA were not eligible to participate in this survey.

Respondents who participated in previous waves of the survey (12-month TIRF REMS Access Program Assessment or the 24-month TIRF REMS Access Program Assessment) were not eligible to participate.

3.1.2 Recruitment

Patients were recruited via a direct letter program. Patients' invitation letters (Appendix A) informed patients that participants who completed the survey and who provided their contact information would be mailed a $50 gift card to thank them for their participation. The thank you letter included the correct answers to key risk message questions, and a copy of the product-specific Medication Guide.

Patients were recruited through a national pharmacy network partner and a Pharmacy Benefits Manager (PBM). All patients who filled one or more prescriptions during the 120 days prior to 18 August 2014 were invited to participate.

3.1.2.1 Direct Letter Program

Patients were recruited via a letter of invitation sent through the United States Postal Service (USPS). The required number of completed surveys was not achieved within approximately 10 days after the first mailing; therefore, subsequent mailings were sent to non-respondents from the original sample to maximize participation.

3.2 Questions and Statements on Key Risk Messages

The questions and statements comprising the knowledge survey were constructed to test the patients' understanding of the key risk messages of the REMS. The questions were to be answered either by selecting options from multiple-choice lists that include statements of the specific key risk messages or by choosing "Yes" or "True," "No" or "False," or "I don't know" regarding statements about TIRF medicines.

For statements or questions that had "True" or "Yes" vs. "False" or "No" response options, the desired response for key risk messages was generally "True" or "Yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions were formatted to have the respondent disagree with the statement as written by providing response options of "False" or "No" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

3.2.1 Key Risk Message 1

Key Risk Message 1 refers to the patient's/caregiver's knowledge that TIRF medicines can cause life-threatening breathing problems.

Key Risk Message 1: TIRF medicines can cause life-threatening breathing problems that can lead to death.		
Question No.	**Question**	**Desired response**
13	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13d	TIRF medicines can cause life-threatening breathing problems that can lead to death.	***True***

3.2.2 Key Risk Message 2

Key Risk Message 2 refers to the patient's/caregiver's awareness that TIRF medicines should be taken only by opioid-tolerant adult patients.

Key Risk Message 2: Patients should not take TIRF medicines if they are not opioid tolerant.		
Question No.	**Question**	**Desired response**
	Please answer True, False, or I don't know for the following statement:	
11	TIRF medicines should only be taken by patients who are opioid tolerant.	***True***
12	Please answer True, False, or I don't know for each of the following statements.	
12a	Opioid tolerant means that a patient is already taking other opioid pain medicines around the clock and their body is used to these medicines.	***True***
13	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13b	It is OK for patients to take TIRF medicines for headache pain.	***False***

3.2.3 Key Risk Message 3

Key Risk Message 3 refers to the patient's/caregiver's knowledge that TIRF medicines should be taken exactly as prescribed by the healthcare provider.

Key Risk Message 3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12b	If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.	***True***
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13c	TIRF medicines should be taken exactly as prescribed by the doctor.	***True***
17b	It is OK to take TIRF medicines for short-term pain that will go away in a few days.	***False***

3.2.4 Key Risk Message 4

Key Risk Message 4 refers to the patient's knowledge of the interchangeability of TIRF medicines.

Key Risk Message 4: Patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12c	It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	***False***

3.2.5 Key Risk Message 5

Key Risk Message 5 refers to the patient's/caregiver's awareness that TIRF medicines should not be given to anyone else even if they have the same symptoms.

Key Risk Message 5: Patients should not give TIRF medicines to anyone else even if they have the same symptoms.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12d	A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	***False***
17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17a	Selling or giving away TIRF medicines is against the law.	***True***

3.2.6 Key Risk Message 6

Key Risk Message 6 refers to the patient's/caregiver's knowledge that TIRF medicines should be stored in a safe place away from children and properly disposed.

Key Risk Message 6: TIRF medicines should be stored in a safe place away from children and properly disposed.		
Question No.	**Question**	**Desired response**
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13a	TIRF medicines should be stored in a safe place out of the reach of children.	***True***
17c	TIRF medicines must be disposed of as described in the specific product's Medication Guide.	***True***
17e	A TIRF medicine can cause an overdose and death in any child who takes it.	***True***
14	What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)	***Get emergency help right away.***

4. STATISTICAL METHODS

4.1 Study Population

4.1.1 Primary Analysis Population

The primary population for analysis was all eligible patients who completed the survey. Eligible patients were defined as those respondents who answered ***Yes*** to Question 1 (agree to take part in survey), ***Yes*** to Question 2 (filled a prescription for a TIRF medicine in the last 4 months) ***or Yes*** to Question 3 (Caregiver for someone who had filled a prescription for a TIRF medicine in the last 4 months), ***No*** to Question 5 (participated in past survey), ***selected an age group ≥18 years of age*** for Question 6 (patient and caregiver), and ***No*** to Question 8 (worked for a TRIG company, UBC, or FDA).

A completed survey was a survey in which all questions as appropriate were answered. Some questions may not have been answered by respondents due to skip logic in the survey questionnaire.

4.1.2 Sub-groups of Interest

The following sub-group analyses of responses to key risk messages were conducted when the sub-group included at least 20 respondents.

Sub-group analysis 1: Reading Medication Guide (Question 18, Question 23, and Question 24):

- S-1a - Respondents who got the Medication Guide and read at least most of it
- S-1b - Respondents who did not get a Medication Guide or answered, "I don't know" or who got a Medication Guide and read only some of it or answered, "I don't know."

Sub-group analysis 2: Understanding of Medication Guide (Question 25):

- S-2a - Respondents who understood all of it or most of it
- S-2b - Respondents who understood some of it
- S-2c - Respondents who answered None or "I don't know"
- S-2d - Respondents who answered, "I don't know" to receipt or reading of the Medication Guide.

Sub-group analysis 3: Time to complete survey - Internet:

- S-3a - <10 min
- S-3b - 10 to<20 min
- S-3c - ≥20 min

Sub-group analysis 4: Time to complete survey - Telephone:

- S-4a - <10 min
- S-4b - 10 to <20 min
- S-4c - ≥20 min

Sub-group analysis 5: Modality to complete survey:

- S-5a - Internet
- S-5b – Telephone

Sub-group analysis 6: Highest level of education (Question 37):

- S-6a – Less than, Some, or High school graduate/GED or prefer not to answer
- S-6b - Some college or associate's degree
- S-6c - Bachelor's degree or Master's degree
- S-6d - Professional or Doctoral degree

Sub-group analysis 7: Age group of respondent (Question 6):

- S-7a – 18 to 39
- S-7b – 40 to 49
- S-7c – 50 to 59
- S-7d – 60 or older

Results of sub-group analyses performed are provided in Appendix B, Tables 6.1, 7.1, 7.2, 8.1, 8.2, 9.1, 10.1, 10.2, 11.1, and 11.2. Answers from caregivers and answers from patients were combined for the sub-group analysis.

4.1.2.1 Primary Analyses

Primary analyses were done for all key risk messages. The primary analysis for a key risk message evaluated the number and percentage of each correct response for each individual question/item defined by the key risk message. The correct response to each question/item is included in the body of the risk message table (Section 3.3).

4.1.2.2 Secondary Analyses

Secondary analyses evaluated the number and percentages of correct responses and the average of correct responses within the risk message overall to assess understanding of the comprehensive key risk message. A correct response rate of 65% or greater was considered to represent adequate understanding of each concept or key risk message.

4.1.3 Patient Report of an Adverse Event, Product Complaint, or Medical Information Request during the Survey

A patient or caregiver may have reported an adverse event or product complaint while taking the online survey in the free text field of the Internet-based survey. Patients or caregivers who opted for the telephone-based survey may have reported an adverse event or a product complaint while in conversation with the Survey Coordinating Center (SCC). If an event was mentioned to the SCC Associate, the Associate documented the adverse event or product complaint, the verbatim response, and the respondent's contact information, if provided. The respondent was informed that a representative from the appropriate TIRF medicine sponsor might contact them to obtain additional information about the adverse event or product complaint. Internet surveys were monitored for any comments recorded in the free text field. Information on all reports (Internet or telephone) that constituted an adverse event or product complaint was forwarded to the appropriate TIRF medicine sponsor for processing within one business day of awareness of the event as outlined in the Adverse Event/Product Complaint Project Specific Procedure (AE/PC PSP).

5. RESULTS

Results of the patient responses to questions in the KAB survey are summarized in this section, and a full set of responses can be found in Appendix B.

5.1 Survey Participants

5.1.1 Survey Participant Administration Results

Patients were recruited through a national pharmacy chain network partner and a PBM. Prior to mailing out invitation letters, all patients who previously completed the survey were removed. In addition, patients common to both lists were only sent one invitation letter. Based on the number of prescriptions filled during the 120 days prior to survey implementation (18 August 2014), the national pharmacy chain network partner identified 993 possible participants and the PBM identified 350 possible participants among patients and caregivers. All of these possible participants were sent a survey invitation letter. A total of 1,986 reminder letters were sent to non-responders (some potential participants received

more than one reminder letter). Of the 1343 possible participants, 272 respondents accessed the survey and were screened for eligibility; 229 of the 272 (84.2%) respondents met eligibility criteria and completed the survey (Table 1). Of the 229 respondents, 78 (34.1%) completed the survey by telephone, and 151 (65.9%) completed it on the Internet.

Although, the survey had a target of 300 eligible completed responders, the initial population of 1,343 possible participants was small. The response of 229 completed surveys is a participation rate of 17.1% (229/1343). Although, the target of 300 eligible completed surveys was not achieved, a sample of 229 completed surveys is adequate to draw conclusions regarding patient understanding of safe use of TIRF medicines. See Table A below.

Table A: Precision of Estimated Rates with a Sample Size of 229 (2-sided 95% Confidence Interval)

Estimated Rate of Understanding	Estimated Confidence Interval	
50.5%	43.13%	56.44%
55.0%	47.89%	61.16%
60.0%	53.16%	66.23%
65.0%	58.06%	70.81%
70.0%	63.48%	75.74%
75.0%	68.52%	80.17%
80.0%	74.13%	84.90%
85.0%	79.39%	89.12%
90.0%	85.31%	93.53%
95.0%	91.03%	97.26%
100.0%	98.40%	100.0%

Table 1. Survey Participant Administration Results

Summary Statistic	Screened Patients/Caregivers N=272[1]	
	All Respondents	
	n	%
Number of invitations issued to patients/caregivers	1343	
Number of reminder letters issued to patients/caregivers	1986	
Number of patients/caregivers screened for participation	272 [1]	
Number of patients/caregivers eligible for participation	229 [2]	84.2
Number of eligible respondents completing the survey	229	100.0
Method of Survey Completion		
Number of surveys completed by telephone	78	34.1[3]
Number of surveys completed by internet	151	65.9[3]

[1] The denominator for the percentages of eligible patients/caregivers is the number of screened patients/caregivers (N=272).

[2] The denominator for percentages of eligible patients/caregivers completing the survey is the number of eligible patients. (N=229).

[3] The denominator for percentages completed by telephone or Internet is the number of eligible patients/caregivers who completed the survey (N=229).

Of the 272 respondents (Table 1), the screening procedure identified 229 eligible participants (including 225 patients and 4 caregivers) all of whom completed the survey (Table 2). Due to the small (n=4) number of caregivers participating in the survey, the majority of results are reported for patients and caregivers combined.

As shown in Table 2, a total of 272 patients/caregivers agreed to participate in this survey. During the screening process it was determined 43 (15.8%) respondents were not eligible to participate in the survey because they either indicated that they had not filled a prescription for a TIRF medicine within the last 4 months either for themselves or as a the caregiver of a patient, that they had participated in or did not know whether they participated in a survey about TIRF medicines before, or that they or an immediate family member had worked for a TRIG company, the FDA, or UBC.

Thus, there were 229 eligible participants (including four caregivers), all of whom completed the survey (Table 2).

Table 2. Survey Participant Screening Results

Question	Screened Patients/Caregivers N=272		Eligible and Complete Respondents N=229	
	n	%	n	%
Question 1: Do you agree to participate in this survey?				
Yes	272	100.0	229	100.0
No[1]	0	0.0		
Question 2: Within the last 4 months, have you filled a prescription for yourself for a transmucosal immediate release fentanyl medicine (known as "TIRF medicines")? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of any of these brands.				
Yes	262	96.3	225	98.3
No	9	3.3	4	1.7
I don't know	1	0.4	0	0.0
Question not asked[2]	0	0.0		
Question 3: Are you a caregiver for someone who has filled a prescription for a TIRF medicine within the last 4 months? As a reminder, TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of any of these brands.				
Yes	4	1.5	4	1.7
No[1]	5	1.8		
I don't know[1]	1	0.4		
Question not asked [2]	262	96.3		
Question 5: Have you ever taken part in a survey about a TIRF medicine before?				
Yes[1]	20	7.4		
No	233	85.7	229	100.0
I don't know[1]	13	4.8		
Question not asked [2]	6	2.2		

Table 2. Survey Participant Screening Results

Question	Screened Patients/Caregivers N=272		Eligible and Complete Respondents N=229	
	n	%	n	%
Question 6: Which of the following groups best describes your age?				
Under 18[1]	0	0.0		
18 – 29	4	1.5	4	1.7
30 – 39	26	9.6	26	11.4
40 – 49	65	23.9	65	28.4
50 – 59	91	33.5	88	38.4
60 – 69	38	14.0	38	16.6
70 or older	8	2.9	8	3.5
Prefer not to answer[1]	1	0.4		
Question not asked [2]	39	14.3		
Question 7: Which of the following groups best describes the patient's age? (Caregivers, only)				
Under 16	0	0.0		
16 – 29	0	0.0	0	0.0
30 – 39	0	0.0	0	0.0
40 – 49	3	1.1	3	1.3
50 – 59	0	0.0	0	0.0
60 – 69	1	0.4	1	0.4
70 or older	0	0.0	0	0.0
Prefer not to answer	0	0.0		
Question not asked[2]	268	98.5		

Table 2. Survey Participant Screening Results

Question	Screened Patients/Caregivers N=272		Eligible and Complete Respondents N=229	
	n	%	n	%
Question 8: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.[3]				
Anesta LLC.[1]	0	0.0		
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) [1]	0	0.0		
Depomed, Inc.[1]	0	0.0		
Galena Biopharma [1]	0	0.0		
Insys Therapeutics[1]	0	0.0		
Mallinckrodt Pharmaceuticals[1]	1	0.4		
McKesson Specialty Care Solutions[1]	0	0.0		
Meda Pharmaceuticals[1]	0	0.0		
Mylan, Inc.[1]	0	0.0		
Par Pharmaceutical, Inc.[1]	0	0.0		
RelayHealth[1]	0	0.0		
Teva Pharmaceuticals, Ltd.[1]	0	0.0		
United BioSource Corporation[1]	0	0.0		
FDA[1]	1	0.4		
No[4]	229	84.2	229	100.0
I don't know[1]	1	0.4		

[1] Ineligible to participate in the survey.
[2] Question not asked due to previous question elimination.
[3] More than one response can be selected, so percentages may not sum to 100%.
[4] Ineligible if selected in addition to another response.

Of the 229 patient/caregivers, 78 (34.1%) completed the survey by telephone, and 151 (65.9%) completed it on the Internet (Table 3). Those taking the survey online took an average of 13.1 minutes to complete it, while those taking it by telephone took an average of 20.8 minutes.

Table 3. Time to Complete Survey for Completers (Minutes)

Time to Complete Survey for Completers (Minutes)			
Summary Statistic	**Telephone**	**Internet**	**Total[1]**
N	78	151	229
Mean (± SD)	20.8 (6.20)	13.1 (5.61)	15.7 (6.87)
Minimum	13	5	5
Median	18.9	11.7	15.0
Maximum	50	41	50
Category			
0 – <5 Minutes	0	1	1
5 – <10 Minutes	0	49	49
10 – <15 Minutes	6	60	66
15 – <20 Minutes	41	21	62
20 – <25 Minutes	15	17	32
25 – <30 Minutes	10	1	11
30 Minutes or More	6	2	8

[1] Number of eligible respondents completing the survey (Table 1).

SD = Standard Deviation

5.1.2 Patient/Caregiver Demographics

The demographic characteristics of respondents who completed the survey are shown in Table 4. The largest number of respondents (n=153; 66.8%) were in the 40– 59 years age group, the majority of respondents (n=136, 59.4%) were females, and 187 (81.6%) respondents had at least some college or an Associate's degree or higher education. Most prescriptions filled in the 4 months preceding the survey included 112 (48.9%) for Actiq® (including generic versions), 59 (25.8%) for Subsys, and 55 (24.0%) for Fentora®. Most participants (n=83; 36.2%) were from the South, followed by the Northeast (n=55; 24.0%), West (n=51; 22.3%), and Midwest (n=40; 17.5%) regions of the United States (US) (Table 4).

Table 4. Demographic Characteristics of Eligible Patients/Caregivers

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	%	n	%	n	%
Question 4: For which TIRF medicines have you filled a prescription in the last 4 months. Please select all that apply. [2]						
Abstral	6	2.7	0	0.0	6	2.6
Actiq, including generic versions of Actiq	110	48.9	2	50.0	112	48.9
Fentora	54	24.0	1	25.0	55	24.0
Lazanda	0	0.0	0	0.0	0	0.0
Onsolis	0	0.0	0	0.0	0	0.0
Subsys	57	25.3	2	50.0	59	25.8
Other	8	3.6	0	0.0	8	3.5
I don't know	3	1.3	0	0.0	3	1.3
Question 6: Which of the following groups best describes your age?						
18 – 29	4	1.8	0	0.0	4	1.7
30 – 39	26	11.6	0	0.0	26	11.4
40 – 49	61	27.1	4	100.0	65	28.4
50 – 59	88	39.1	0	0.0	88	38.4
60 – 69	38	16.9	0	0.0	38	16.6
70 or older	8	3.6	0	0.0	8	3.5
Question 36: What is your gender?						
Male	90	40.0	2	50.0	92	40.2
Female	134	59.6	2	50.0	136	59.4
Prefer not to answer	1	0.4	0	0.0	1	0.4

Table 4. Demographic Characteristics of Eligible Patients/Caregivers

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	%	n	%	n	%
Question 37: What is the highest level of education you have completed?						
Less than high school	0	0.0	0	0.0	0	0.0
Some high school	5	2.2	0	0.0	5	2.2
High School graduate/GED	36	16.0	1	25.0	37	16.2
Some college/Associate's degree	102	45.3	0	0.0	102	44.5
Bachelor's degree	47	20.9	2	50.0	49	21.4
Master's degree	22	9.8	0	0.0	22	9.6
Professional or Doctoral degree	13	5.8	1	25.0	14	6.1
Prefer not to answer	0	0.0	0	0.0	0	0.0
Question 38: What is the main language you speak at home? (Please select only one)						
English	224	99.6	4	100.0	228	99.6
French	0	0.0	0	0.0	0	0.0
Spanish	1	0.4	0	0.0	1	0.4
Portuguese	0	0.0	0	0.0	0	0.0
Italian	0	0.0	0	0.0	0	0.0
German	0	0.0	0	0.0	0	0.0
Chinese	0	0.0	0	0.0	0	0.0
Japanese	0	0.0	0	0.0	0	0.0
Korean	0	0.0	0	0.0	0	0.0
Other	0	0.0	0	0.0	0	0.0
Prefer not to answer	0	0.0	0	0.0	0	0.0
Question 39: Are you Hispanic or Latino?						
Yes	7	3.1	1	25.0	8	3.5
No	216	96.0	3	75.0	219	95.6
Prefer not to answer	2	0.9	0	0.0	2	0.9

Table 4. Demographic Characteristics of Eligible Patients/Caregivers

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	%	n	%	n	%
Question 40: For informational purposes only, indicate which of the following U.S. census categories best describes your race?						
American Indian or Alaska Native	3	1.3	0	0.0	3	1.3
Asian (origins of Far East, Southeast Asia or the Indian subcontinent)	0	0.0	0	0.0	0	0.0
Black or African American	9	4.0	0	0.0	9	3.9
Native Hawaiian or Other Pacific Islander	0	0.0	0	0.0	0	0.0
White	198	88.0	3	75.0	201	87.8
Two or more races	6	2.7	0	0.0	6	2.6
Other	3	1.3	1	25.0	4	1.7
Prefer not to answer	6	2.7	0	0.0	6	2.6
Geographic Distribution (based on Question 41 – State or US Territory)[2]						
Northeast	54	24.0	1	25.0	55	24.0
Midwest	39	17.3	1	25.0	40	17.5
South	81	36.0	2	50.0	83	36.2
West	51	22.7	0	0.0	51	22.3
Other	0	0.0	0	0.0	0	0.0
Prefer not to answer	0	0.0	0	0.0	0	0.0

[1] Number of eligible respondents completing the survey (See Table 1).

[2] More than one response can be selected, so percentages may not sum to 100%.

[3] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

5.1.3 TIRF Medicines Education Materials

Respondents were asked about their awareness of educational materials for TIRF medicines, specifically the Medication Guide (Table 5), and the Patient-Prescriber Agreement Form

(Table 6). Of the 229 respondents, 217 (94.8%) reported they had received the Medication Guide for the TIRF medicine prescribed to them. Of these, 122 respondents (56.2%) reported receiving the Medication Guide from their doctor or doctor's office with 102 of the respondents (83.6%) receiving it at the first appointment with the prescribing doctor; and 193 respondents (88.9%) received it from their pharmacy with 172 of the respondents (89.1%) stating they received the Medication Guide each time a prescription was filled. Most respondents who received the Medication Guide indicated they read the Medication Guide (n=209; 96.3%); of these, 193 respondents (92.3%) read all or most of it, and 184 (88.0%) respondents indicated understanding all or most of the Medication Guide. There were 130 respondents (59.9%) who indicated someone offered to explain the medication guide to them; of these, 91 respondents (70.0%) indicated the doctor or someone in the doctor's office offered to explain the Medication Guide and 102 respondents (78.5%) indicated their pharmacist offered to explain the Medication Guide.

Table 5. Responses to Questions About TIRF Medication Guides

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	%	n	%	n	%
Question 18: Have you ever received a Medication Guide for the TIRF medicine that was prescribed for you?						
Yes	213	94.7	4	100.0	217	94.8
No	9	4.0	0	0.0	9	3.9
I don't know	3	1.3	0	0.0	3	1.3
Question 19: Did you receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?[2]						
Yes	122	57.3	0	0.0	122	56.2
No	74	34.7	4	100.0	78	35.9
I don't know	17	8.0	0	0.0	17	7.8
N/A (answered ***No*** or ***I don't know*** to Question 18)	12		0		12	
Question 20: When was the Medication Guide given to you? Please select all that apply.[2, 3]						
At the first appointment with the doctor who prescribed the TIRF medicine	102	83.6	0	0.0	102	83.6
At the last appointment with the doctor who prescribed the TIRF medicine	24	19.7	0	0.0	24	19.7

Table 5. Responses to Questions About TIRF Medication Guides

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	%	n	%	n	%
I don't remember	17	13.9	0	0.0	17	13.9
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 19)	103		4		107	
Question 21: Did you receive the Medication Guide for the TIRF medicine from the pharmacy?[2]						
Yes	189	88.7	4	100.0	193	88.9
No	14	6.6	0	0.0	14	6.5
I don't know	10	4.7	0	0.0	10	4.6
N/A (answered ***No*** or ***I don't know*** to Question 18)	12		0		12	
Question 22: How frequently do you receive a Medication Guide for the TIRF medicine at the pharmacy? [2]						
Only with the first filled prescription	7	3.7	0	0.0	7	3.6
Each time a prescription is filled	168	88.9	4	100.0	172	89.1
Other[4]	6	3.2	0	0.0	6	3.1
I don't know	8	4.2	0	0.0	8	4.1
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 21)	36		0		36	
Question 23: Did you read the Medication Guide? [2]						
Yes	207	97.2	2	50.0	209	96.3
No	5	2.3	2	50.0	7	3.2
I don't know	1	0.5	0	0.0	1	0.5

Table 5. Responses to Questions About TIRF Medication Guides

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	%	n	%	n	%
N/A (answered ***No*** or ***I don't know*** to Question 18)	12		0		12	
Question 24: How much did you read? [2]						
All of it	123	59.4	2	100.0	125	59.8
Most of it	68	32.9	0	0.0	68	32.5
Some of it	16	7.7	0	0.0	16	7.7
I don't know	0	0.0	0	0.0	0	0.0
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 23)	18		2		20	
Question 25: How much of the Medication Guide did you understand?[2]						
All of it	102	49.3	0	0.0	102	48.8
Most of it	80	38.6	2	100.0	82	39.2
Some of it	25	12.1	0	0.0	25	12.0
None of it	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 23)	18		2		20	
Question 26: Did someone offer to explain the Medication Guide to you?[2]						
Yes	128	60.1	2	50.0	130	59.9
No	74	34.7	1	25.0	75	34.6
I don't know	11	5.2	1	25.0	12	5.5
N/A (answered ***No*** or ***I don't know*** to Question 18)	12		0		12	

Table 5. Responses to Questions About TIRF Medication Guides

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	%	n	%	n	%
Question 27: Who offered to explain the Medication Guide to you? Please select all that apply [2,3]						
The doctor or another healthcare professional in the doctor's office	90	70.3	1	50.0	91	70.0
The pharmacist where the TIRF medicine prescription was filled	100	78.1	2	100.0	102	78.5
Someone else (specify the type of person but not his/her name)[5]	10	7.8	0	0.0	10	7.7
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 26)	97		2		99	
Question 28: Did you accept the offer to have the Medication Guide explained to you?[2]						
Yes	73	57.0	1	50.0	74	56.9
No	53	41.4	1	50.0	54	41.5
I don't know	2	1.6	0	0.0	2	1.5
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 26)	97		2		99	
Question 29: How much of the explanation did you understand? [2]						
All of it	48	65.8	1	100.0	49	66.2
Most of it	23	31.5	0	0.0	23	31.1
Some of it	2	2.7	0	0.0	2	2.7
None of it	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0

Table 5. Responses to Questions About TIRF Medication Guides

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	%	n	%	n	%
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 26 or ***No*** or ***I don't know*** to Question 28)	152		3		155	
Question 30: Did you or do you have any questions about the information in the Medication Guide?[2]						
Yes[6]	15	7.0	0	0.0	15	6.9
No	196	92.0	4	100.0	200	92.2
I don't know	2	0.9	0	0.0	2	0.9
N/A (answered ***No*** or ***I don't know*** to Question 18)	12		0		12	

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

[3] More than one response can be selected, so percentages may not sum to 100%.

[4] Verbatim text for 'other' for how frequently the Medication Guide is received from the pharmacy (Question 22) are presented in Listing 1.

[5] Verbatim text for other persons offering to explain the Medication Guide (Question 27) are presented in Listing 2.

[6] Questions about the information in the Medication Guide (Question 30) are presented in Listing 3.

NA = Not Applicable

The responses to Questions 22, 27 and 30 are listed in Listing 1, Listing 2, and Listing 3, respectively.

5.1.4 Patient-Prescriber Agreement Form

After respondents were asked the questions regarding the key risk messages, they were asked if they had received, read, and understood the PPAF. A total of 178 respondents (77.7%) indicated that someone at the doctor's office had explained the PPAF to them, and of these, 140 respondents (78.7%) understood all of it and 33 (18.5%) understood most of it. The PPAF was signed by 179 respondents (78.2%); of these, 137 responders (76.5%) reported receiving a copy of the signed PPAF (Table 6).

Table 6. Responses to Questions About the Patient-Prescriber Agreement Form

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	%	n	%	n	%
Question 32: Did the doctor or someone in the doctor's office explain the Patient-Prescriber Agreement Form to you?						
Yes	176	78.2	2	50.0	178	77.7
No	27	12.0	1	25.0	28	12.2
I don't know	22	9.8	1	25.0	23	10.0
Question 33: How much of the explanation did you understand?[2]						
All of it	139	79.0	1	50.0	140	78.7
Most of it	32	18.2	1	50.0	33	18.5
Some of it	3	1.7	0	0.0	3	1.7
None of it	0	0.0	0	0.0	0	0.0
I don't know	2	1.1	0	0.0	2	1.1
N/A (answered ***No*** or ***I don't know*** to Question 32)	49		2		51	
Question 34: Did you sign a Patient-Prescriber Agreement Form?						
Yes	176	78.2	3	75.0	179	78.2
No	17	7.6	1	25.0	18	7.9
I don't know	32	14.2	0	0.0	32	14.0
Question 35: Did the doctor or someone in the doctor's office give you a copy of the signed Patient-Prescriber Agreement Form?[2]						
Yes	134	76.1	3	100.0	137	76.5
No	22	12.5	0	0.0	22	12.3
I don't know	20	11.4	0	0.0	20	11.2
N/A (answered ***No*** or ***I don't know*** to Question 34)	49		1		50	

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

NA = Not Applicable

5.2 KAB Survey Objectives

5.2.1 Key Risk Message Results

The focus of this section of the document is on the findings for the total respondent population (patients plus caregivers).

5.2.1.1 Key Risk Message 1

Key Risk Message 1 refers to the patient's/caregiver's knowledge that TIRF medicines can cause life-threatening breathing problems that can lead to death.

Analysis of responses to Question 13d for Key Risk Message 1 showed that 209 (91.3%) of the 229 eligible respondents were aware of the risk of life-threatening breathing problems with TIRF medicines (Table 7).

Table 7. Key Risk Message 1: TIRF Medicines Can Cause Life-Threatening Breathing Problems That Can Lead to Death

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	n	% (95% CI)[3]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you / the patient.						
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.						
True[2]	205	91.1 (86.6, 94.5)	4	100.0 (39.8, 100.0)	209	91.3 (86.8, 94.6)
False	1	0.4	0	0.0	1	0.4
I don't know	19	8.4	0	0.0	19	8.3

[1] Number of eligible respondents completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or component within a question.
[3] All confidence intervals are exact binomial 95% confidence intervals.

5.2.1.2 Key Risk Message 2

Key Risk Message 2 refers to the patient's/caregiver's knowledge that they should not take TIRF Medicines if they are not opioid tolerant. Three questions defined this key risk message (Table 8).

In response to the statement in Question 11 that TIRF medicines should only be taken by patients who are opioid tolerant, 195 respondents (85.2%) gave the correct (*True*) response.

The majority of respondents (n=187; 81.7%) also understood that opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines (Question 12a). In response to Component 13b, 159 (69.4%) knew that it is not okay for patients to-take TIRF medicines for headache pain, while 54 respondents (23.6%) selected the "I don't know" option. Of the 159 respondents who correctly answered Component 13b (*"It is OK for patients to take TIRF medicines for headache pain)*, 141 respondents had read most of the Medication Guide and 18 respondents had read some or none of it (see Table 14).

Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 2.4 (one-sided 95% confidence interval [CI] 2.2, 3.0) out of a possible 3 (Table 8).

Table 8. Key Risk Message 2: Patients Should Not Take TIRF Medicines If They Are Not Opioid Tolerant

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	n	% (95% CI)[3]
Question 11: Please answer True, False, or I don't know for the following statement:						
TIRF medicines should only be taken by patients who are opioid tolerant.						
True[2]	191	84.9 (79.5, 89.3)	4	100.0 (39.8, 100.0)	195	85.2 (79.9, 89.5)
False	6	2.7	0	0.0	6	2.6
I don't know	28	12.4	0	0.0	28	12.2
Question 12: Please answer True, False, or I don't know for the following statements:						
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around the clock and their body is used to these medicines.						
True[2]	183	81.3 (75.6, 86.2)	4	100.0 (39.8, 100.0)	187	81.7 (76.0, 86.5)
False	19	8.4	0	0.0	19	8.3
I don't know	23	10.2	0	0.0	23	10.0

Table 8. Key Risk Message 2: Patients Should Not Take TIRF Medicines If They Are Not Opioid Tolerant

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	n	% (95% CI)[3]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13b: It is OK for patients to take TIRF medicines for headache pain.						
True	16	7.1	0	0.0	16	7.0
False[2]	157	69.8 (63.3, 75.7)	2	50.0 (6.8, 93.2)	159	69.4 (63.0, 75.3)
I don't know	52	23.1	2	50.0	54	23.6
Secondary Analyses: Demonstrated Understanding						
0 correct responses	10	4.4	0	0.0	10	4.4
1 correct response	21	9.3	0	0.0	21	9.2
2 correct responses	72	32.0	2	50.0	74	32.3
3 correct responses	122	54.2	2	50.0	124	54.1
Average number of correct responses	2.4 (2.2, 3.0)[4]		2.5 (1.2, 3.0)[4]		2.4 (2.2, 3.0)[4]	

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Indicates the correct response(s) to each question or component within a question.

[3] All confidence intervals are exact binomial 95% confidence intervals.

[4] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.1.3 Key Risk Message 3

Key Risk Message 3 refers to the patient's/caregiver's knowledge that TIRF medicines should be taken exactly as prescribed by the healthcare provider. Three questions define this key risk message (Table 9). In response to Question 12b, 84 respondents (36.7%) understood that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine while 58 (25.3%) answered incorrectly and 87 (38.0%) selected the "I don't know" option. Of the 84 respondents who gave the correct response, 79 (40.9%) read most of the Medication Guide while 5 (13.9%) read some or none of the Medication Guide. Of the 58 respondents who answered this question incorrectly, 46 (23.8%) had read most of the Medication Guide and of the 87 respondents who selected the "I don't know" response, 68 (35.2%) had read most of the Medication Guide (see Table 14).

Responding to Component 13c, 227 respondents (99.1%) understood that TIRF medicines should be taken exactly as prescribed by the doctor, and 190 (83.0%) knew that is not all right to take TIRF medicines for short-term pain that will go away in a few days (Component 17b).

Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 2.2 (one-sided 95% CI 2.0, 3.0) out of a possible 3 (Table 9).

Table 9. Key Risk Message 3: TIRF Medicines Should Be Taken Exactly As Prescribed By The Healthcare Provider

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	n	% (95% CI)[3]
Question 12: Please answer True, False, or I don't know for each of the following statements.						
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.						
True[2]	83	36.9 (30.6, 43.6)	1	25.0 (0.6, 80.6)	84	36.7 (30.4, 43.3)
False	57	25.3	1	25.0	58	25.3
I don't know	85	37.8	2	50.0	87	38.0
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13c: TIRF medicines should be taken exactly as prescribed by the doctor.						
True[2]	223	99.1 (96.8, 99.9)	4	100.0 (39.8, 100.0)	227	99.1 (96.9, 99.9)
False	2	0.9	0	0.0	2	0.9
I don't know	0	0.0	0	0.0	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you / the patient.						
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.						
True	12	5.3	0	0.0	12	5.2
False[2]	186	82.7 (77.1, 87.4)	4	100.0 (39.8, 100.0)	190	83.0 (77.5, 87.6)

Table 9. Key Risk Message 3: TIRF Medicines Should Be Taken Exactly As Prescribed By The Healthcare Provider

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	n	% (95% CI)[3]
I don't know	27	12.0	0	0.0	27	11.8
Secondary Analysis: Demonstrated Understanding						
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	30	13.3	0	0.0	30	13.1
2 correct responses	123	54.7	3	75.0	126	55.0
3 correct responses	72	32.0	1	25.0	73	31.9
Average number of correct responses	2.2 (2.0, 3.0)[4]		2.3 (1.0, 3.0)[4]		2.2 (2.0, 3.0)[4]	

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Indicates the correct response(s) to each question or component within a question.

[3] All confidence intervals are exact binomial 95% confidence intervals.

[4] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.1.4 Key Risk Message 4

Key Risk Message 4 refers to the patient's/caregiver's knowledge that they must not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider (Table 10).

Of the 229 respondents, 222 (96.9%) understood that it is not safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.

Table 10. Risk Message 4: Patients Should Not Switch From a TIRF Medicine to Another Medicine That Contains Fentanyl Without Talking to a Healthcare Provider

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	n	% (95% CI)[3]
Question 12: Please answer True, False, or I don't know for each of the following statements.						
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first						
True	2	0.9	0	0.0	2	0.9
False[2]	218	96.9 (93.7, 98.7)	4	100.0 (39.8, 100.0)	222	96.9 (93.8, 98.8)
I don't know	5	2.2	0	0.0	5	2.2

[1] Number of eligible respondents completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or component within a question.
[3] All confidence intervals are exact binomial 95% confidence intervals.

5.2.1.5 Key Risk Message 5

Key Risk Message 5 refers to patient's/caregiver's knowledge that TIRF medicines should not be given to anyone else even if they have the same symptoms (Table 11).

For Component 12d, 227 respondents (99.1%) understood that a patient may not give TIRF medicines to another person if they have the same symptoms as the patient, and 227 respondents (99.1%) understood that selling or giving away TIRF medicines is against the law (Component 17a).

Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 2.0 (one-sided 95% CI 1.8, 2.0) out of a possible 2 (Table 11).

Table 11. Key Risk Message 5: Patients Should Not Give TIRF Medicines to Anyone Else Even if They Have the Same Symptoms

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	n	% (95% CI)[3]
Question 12: Please answer True, False, or I don't know for each of the following statements.						
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.						
True	1	0.4	0	0.0	1	0.4
False[2]	223	99.1 (96.8, 99.9)	4	100.0 (39.8, 100.0)	227	99.1 (96.9, 99.9)
I don't know	1	0.4	0	0.0	1	0.4
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17a: Selling or giving away TIRF medicines is against the law.						
True[2]	223	99.1 (96.8, 99.9)	4	100.0 (39.8, 100.0)	227	99.1 (96.9, 99.9)
False	1	0.4	0	0.0	1	0.4
I don't know	1	0.4	0	0.0	1	0.4
Secondary Analysis: Demonstrated Understanding						
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	4	1.8	0	0.0	4	1.7
2 correct responses	221	98.2	4	100.0	225	98.3
Average number of correct responses	2.0 (1.8, 2.0)[4]		2.0 (0.8, 2.0)[4]		2.0 (1.8, 2.0)[4]	

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Indicates the correct response(s) to each question or component within a question.

[3] All confidence intervals are exact binomial 95% confidence intervals.

[4] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.1.6 Key Risk Message 6

Key Risk Message 6 refers to the patient's/caregiver's knowledge that TIRF medicines should be stored in a safe place away from children and properly disposed (Table 12).

Component 13a elicited the correct (*True*) response from 227 respondents (99.1%) who were knowledgeable that TIRF medicines should be stored in a safe place out of the reach of children. In addition, 215 respondents (93.9%) understood that TIRF medicines must be disposed of as described in the specific product's Medication Guide (Component 17c). Also, most respondents (n=207; 90.4%) understood that a TIRF medicine can cause an overdose and death in any child who takes it (Component 17e); and that they should get emergency help right way (n=202; 88.2%) if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine (Question 14)

Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 3.7 (one-sided 95% CI 3.5, 4.0) out of a possible 4 (Table 12).

Table 12. Key Risk Message 6: TIRF Medicines Should be Stored in a Safe Place Away From Children and Properly Disposed

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	n	% (95% CI)[3]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13a: TIRF medicines should be stored in a safe place out of the reach of children.						
True[2]	223	99.1 (96.8, 99.9)	4	100.0 (39.8, 100.0)	227	99.1 (96.9, 99.9)
False	1	0.4	0	0.0	1	0.4
I don't know	1	0.4	0	0.0	1	0.4
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.						
True[2]	211	93.8 (89.8, 96.6)	4	100.0 (39.8, 100.0)	215	93.9 (90.0, 96.6)
False	0	0.0	0	0.0	0	0.0
I don't know	14	6.2	0	0.0	14	6.1
17e: A TIRF medicine can cause an overdose and death in any child who takes it.						
True[2]	203	90.2 (85.6, 93.8)	4	100.0 (39.8, 100.0)	207	90.4 (85.8, 93.9)
False	2	0.9	0	0.0	2	0.9
I don't know	20	8.9	0	0.0	20	8.7

Table 12. Key Risk Message 6: TIRF Medicines Should be Stored in a Safe Place Away From Children and Properly Disposed

Question	Patients N=225		Caregivers N=4		Patients & Caregivers N=229[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	n	% (95% CI)[3]
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)						
Get emergency help right away[2]	198	88.0 (83.0, 91.9)	4	100.0 (39.8, 100.0)	202	88.2 (83.3, 92.1)
Do nothing	0	0.0	0	0.0	0	0.0
Wait an hour and see if the person is OK	7	3.1	0	0.0	7	3.1
I don't know	20	8.9	0	0.0	20	8.7
Secondary Analyses: Demonstrated Understanding						
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	2	0.9	0	0.0	2	0.9
2 correct responses	9	4.0	0	0.0	9	3.9
3 correct responses	41	18.2	0	0.0	41	17.9
4 correct responses	173	76.9	4	100.0	177	77.3
Average number of correct responses	3.7 (3.5, 4.0)[4]		4.0 (2.4, 4.0)[4]		3.7 (3.5, 4.0)[4]	

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Indicates the correct response(s) to each question or component within a question.

[3] All confidence intervals are exact binomial 95% confidence intervals.

[4] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.2 Other Survey Questions

5.2.2.1 Additional Questions about TIRF Medicines Safety

Table 13 summarizes the patient/caregiver responses to additional questions about the safe use of TIRF medicines beyond those associated with the key risk messages. The results generally indicate that respondents were aware of most of the precautions needed to ensure safe use of TIRF medicines. See Section 5.2.1 for all key risk message question results.

The majority of respondents (200; 87.3%) indicated a Health Care Professional (HCP) from the doctor's office discussed the risks and possible side effects of the prescribed TIRF medicine while 23 respondents (10.0%) indicated these were not discussed and 6 respondents (2.6%) did not recall having this conversation.

Most respondents understood that TIRF medicines should not be used for headache or migraine pain (179; 78.2%), dental pain (200; 87.3%), and pain after surgery (161; 70.3%). Only 58 respondents (25.3%) indicated they were aware that TIRF medicines are not indicated for long-lasting painful conditions not caused by cancer, however, 151 (65.9%) of the 229 respondents knew that TIRF medicines should be used for breakthrough pain from cancer.

Most respondents (214; 93.4%) indicated that someone in the doctor's office explained how to use the prescribed TIRF medicines and 185 respondents (80.8%) indicated someone in the doctor's office advised them on the proper storage of the prescribed TIRF medicines. The majority (162; 70.7%) were also aware that TIRF medicines are only available through the TIRF REMS Access Program.

Table 13. Responses to Additional Questions about the Safe Use of TIRF Medicines

Question	Patients N=225		Caregivers N=4		Patients & Caregivers[1] N=229	
	n	%	n	%	n	%
Question 9: Did the doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed for you? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands.						
Yes	197	87.6	3	75.0	200	87.3
No	22	9.8	1	25.0	23	10.0
I don't know	6	2.7	0	0.0	6	2.6

Table 13. Responses to Additional Questions about the Safe Use of TIRF Medicines

Question	Patients N=225		Caregivers N=4		Patients & Caregivers[1] N=229	
	n	%	n	%	n	%
Question 10: For which of the following conditions should you use a TIRF medicine?						
10a: Headache or migraine pain						
Yes	25	11.1	0	0.0	25	10.9
No[2]	175	77.8	4	100.0	179	78.2
I don't know	25	11.1	0	0.0	25	10.9
10b: Breakthrough pain from cancer						
Yes[2]	148	65.8	3	75.0	151	65.9
No	70	31.1	1	25.0	71	31.0
I don't know	7	3.1	0	0.0	7	3.1
10c: Dental pain						
Yes	3	1.3	0	0.0	3	1.3
No[2]	197	87.6	3	75.0	200	87.3
I don't know	25	11.1	1	25.0	26	11.4
10d: Pain after surgery						
Yes	43	19.1	1	25.0	44	19.2
No[2]	159	70.7	2	50.0	161	70.3
I don't know	23	10.2	1	25.0	24	10.5
10e: Long-lasting painful conditions not caused by cancer						
Yes	147	65.3	3	75.0	150	65.5
No [2]	58	25.8	0	0.0	58	25.3
I don't know	20	8.9	1	25.0	21	9.2
Question 15: Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for?						
Yes	210	93.3	4	100.0	214	93.4
No	13	5.8	0	0.0	13	5.7
I don't know	2	0.9	0	0.0	2	0.9

Table 13. Responses to Additional Questions about the Safe Use of TIRF Medicines

Question	Patients N=225		Caregivers N=4		Patients & Caregivers[1] N=229	
	n	%	n	%	n	%
Question 16: Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for you?						
Yes	183	81.3	2	50.0	185	80.8
No	36	16.0	2	50.0	38	16.6
I don't know	6	2.7	0	0.0	6	2.6
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17d: TIRF medicines are only available to patients through a special program (called the TIRF REMS Access program).						
True[2]	159	70.7	3	75.0	162	70.7
False	9	4.0	0	0.0	9	3.9
I don't know	57	25.3	1	25.0	58	25.3

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Indicates the correct response(s) to each question or component within a question.

5.2.3 Sub-group Analysis of Responses to Key Risk Messages

To further assess patient/caregiver understanding of key risk messages, sub-group analyses as described in Section 4.1.2 were conducted.

5.2.3.1 Reading the Medication Guide (Sub-group S-1)

Table 14 summarizes correct response rates for the 6 key risk messages by respondents who got the Medication Guide and read at least most of it (sub-group S-1a) and by respondents who did not get a Medication Guide or answered "I don't know," or who got a Medication Guide and read only some of it or answered "I don't know" (sub-group S-1b). Respondents who read all or most of the Medication Guide had a higher correct response rate than those who read some or none of the Medication Guide, or did not know, with the exception of two questions where correct response rate was 99% and 100% for sub-group S-1a and sub-group S1-b, respectively. The largest difference in correct reponse rate between the sub-groups was seen in Key Risk Message 2 (Patients Should Not Take TIRF Medicines If They Are Not Opioid Tolerant) and Key Risk Message 3 (TIRF Medicines Should Be Taken Exactly As Prescribed By The Healthcare Provider).

Overall, the results indicate that respondents who read all or most of the Medication Guide were better informed regarding the safe use of TIRF medicines. Therefore, the Medication Guide is an effective tool to help patients understand the key risk messages based on the goals of the TIRF REMS.

Table 14. Correct Responses and Response Rates to Key Risk Message Questions Based on Extent of Reading of Medication Guide

Key Risk Message #	Question	Correct Response Rates			
		Read Most of the Medication Guide N=193		Read Some or None of the Medication Guide N=36	
		n	%	n	%
1	13d: TIRF medicines can cause life-threatening breathing problems that can lead to death	180	93.3 (88.8, 96.4)	29	80.6 (64.0, 91.8)
2	11: TIRF medicines should only be taken by patients who are opioid tolerant	170	88.1 (82.7, 92.3)	25	69.4 (51.9, 83.7)
	12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines	163	84.5 (78.6, 89.3)	24	66.7 (49.0, 81.4)
	13b: It is OK for patients to take TIRF medicines for headache pain	141	73.1 (66.2, 79.2)	18	50.0 (32.9, 67.1)
3	12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine	79	40.9 (33.9, 48.2)	5	13.9 (4.7, 29.5)
	13c: TIRF medicines should be taken exactly as prescribed by the doctor	193	100.0 (98.1, 100.0)	34	94.4 (81.3, 99.3)
	17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days	168	87.0 (81.5, 91.4)	22	61.1 (43.5, 76.9)
4	12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first	188	97.4 (94.1, 99.2)	34	94.4 (81.3, 99.3)

Table 14. Correct Responses and Response Rates to Key Risk Message Questions Based on Extent of Reading of Medication Guide

Key Risk Message #	Question	Correct Response Rates			
		Read Most of the Medication Guide N=193		Read Some or None of the Medication Guide N=36	
		n	%	n	%
5	12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient	191	99.0 (96.3, 99.9)	36	100.0 (90.3, 100.0)
	17a: Selling or giving away TIRF medicines is against the law	192	99.5 (97.1, 100.0)	35	97.2 (85.5, 99.9)
6	13a: TIRF medicines should be stored in a safe place out of the reach of children	191	99.0 (96.3, 99.9)	36	100.0 (90.3, 100.0)
	17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide	185	95.9 (92.0, 98.2)	30	83.3 (67.2, 93.6)
	17e: A TIRF medicine can cause an overdose and death in any child who takes it	176	91.2 (86.3, 94.8)	31	86.1 (70.5, 95.3)
	14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? Get emergency help right away	173	89.6 (84.4, 93.6)	29	80.6 (64.0, 91.8)

5.2.3.2 All other Sub-group Analyses

For sub-group analysis 2 (Understanding the Medication Guide) respondents who indicated they understood all or most of the Medication Guide had a higher correct response rate for Key Risk Message 2 (Patients Should Not Take TIRF Medicines If They Are Not Opioid Tolerant) and Key Risk Message 3 (TIRF Medicines Should Be Taken Exactly As Prescribed By The Healthcare Provider) compared with those who indicated they understood some of the Medication Guide, indicated "none"/"I don't know" or did not get or read the Medication Guide.

For sub-group analysis 5 (Modality to Complete the Survey), respondents who took the survey via Internet had a higher correct response rate for Key Risk Message 2 and components of Key Risk Message 3.

For sub-group analysis 6 (Highest Level of Education) respondents who had a high school degree or less tended to have a lower correct response rate for Key Risk Message Question 2, and a component of Key Risk Message 3.

For all other sub-group analyses no sub-group-related trends were evident. The full set of sub-group analysis tables is provided in Appendix B.

5.3 Spontaneous Reporting of Adverse Events, Product Complaints, or Medical Information Requests

Among all survey respondents (N=229; Table 1), there were 38 reports of a potential adverse event, product complaint, and/or medical information request associated with the use of TIRF medicines made during a telephone interview or while activating a gift card. (Appendix B, Listing 4).

Respondents who completed the survey online had the option to write in any questions they had in the free-text field. Of the 15 reports made in the free text field of the online survey, 11 were requests for medical information related to adverse events, withdrawal, drug administration, and dosage. The remaining 4 responses were comments that their questions had been answered by the HCP or they had no questions (Appendix B, Listing 3).

5.4 Summary of Correct Responses for Key Risk Messages

The six key risk messages included in the survey included 14 components detailing these key risk messages. A tabulated summary of correct responses for each component is presented in Table 15. Of the 14 components,12 components had a response rate > 80%. The correct response rate for Component 13b (*It is OK for patients to take TIRF medicines for headache pain*) was 69.4% and for Component 12b (*If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine*) was 36.7% which fell below the desired level of understanding of 65% (Table 15).

Table 15. Summary of Correct Responses for Key Risk Messages

Key Risk Message	Question #	Question	Correct Responses	
			N	% (95% CI)
Key Risk Message 1: TIRF medicines can cause life-threatening breathing problems that can lead to death.	13. Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.			
	13d	TIRF medicines can cause life-threatening breathing problems that can lead to death. (*Correct Response "True"*)	209	91.3 (86.8, 94.6)
Key Risk Message 2: Patients should not take TIRF medicines if they are not opioid tolerant.	Please answer True, False, or I don't know for the following statement:			
	11	TIRF medicines should only be taken by patients who are opioid tolerant. (*Correct Response "True"*)	195	85.2 (79.9, 89.5)
	12a	Opioid tolerant means that a patient is already taking other opioid pain medicines around the clock and their body is used to these medicines. (*Correct Response "True"*)	187	81.7 (76.0, 86.5)
	13. Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.			
	13b	It is OK for patients to take TIRF medicines for headache pain. (*Correct Response "False"*)	159	69.4 (63.0, 75.3)
Key Risk Message 3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.	12. Please answer True, False, or I don't know for each of the following statements.			
	12b	If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine. (*Correct Response "True"*)	84	36.7 (30.4, 43.3)

Table 15. Summary of Correct Responses for Key Risk Messages

Key Risk Message	Question #	Question	Correct Responses	
			N	% (95% CI)
	13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
	13c	TIRF medicines should be taken exactly as prescribed by the doctor. (*Correct Response "True"*)	227	99.1 (96.9, 99.9)
	17b	It is OK to take TIRF medicines for short-term pain that will go away in a few days. (*Correct Response "False"*)	190	83.0 (77.5, 87.6)
Key Risk Message 4: Patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.	12	Please answer True, False, or I don't know for each of the following statements.		
	12c	It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first. (*Correct Response "False"*)	222	96.9 (93.8, 98.8)
Key Risk Message 5: Patients should not give TIRF medicines to anyone else even if they have the same symptoms.	12	Please answer True, False, or I don't know for each of the following statements.		
	12d	A patient may give TIRF medicines to another person if they have the same symptoms as the patient. *(Correct Ressponse "False")*	227	99.1 (96.9, 99.9)
	17. Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.			
	17a	Selling or giving away TIRF medicines is against the law. *(Correct Response "True")*	227	99.1 (96.9, 99.9)

Table 15. Summary of Correct Responses for Key Risk Messages

Key Risk Message	Question #	Question	Correct Responses	
			N	% (95% CI)
Key Risk Message 6: TIRF medicines should be stored in a safe place away from children and properly disposed.	13/17. Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.			
	13a	TIRF medicines should be stored in a safe place out of the reach of children. *(Correct Response "True")*	227	99.1 (96.9, 99.9)
	17c	TIRF medicines must be disposed of as described in the specific product's Medication Guide. *(Correct Response "True")*	215	93.9 (90.0, 96.6)
	17e	A TIRF medicine can cause an overdose and death in any child who takes it. *(Correct Response "True")*	207	90.4 (85.8, 93.9)
	14	What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.) *(Correct Response: Get emergency help right away.)*	202	88.2 (83.3, 92.1)

6. FDA FEEDBACK

There was no FDA feedback provided on the 24-month assessment of the TIRF REMS.

7. DISCUSSION, AND CONCLUSIONS

Discussion

For the patient KAB survey, invitations (and reminders) were sent to all known patients/caregivers who had filled a prescription within the 4 months prior to survey launch. From among those who responded to the invitation, 229 patients/caregivers completed the survey (there were only 4 caregivers who participated in the survey). Although, the survey had a target of 300 completed responders, the pool of 1343 patients/caregivers, who were mailed the invitation, was small. The response of 229 completed surveys from this limited pool is within the expected response rate to mailed invitations (17.1%; 229/1343).

The specific goals of the TIRF medicines patient/caregiver KAB survey were to evaluate the level of knowledge and assess the attitudes and behavior of patients/caregivers regarding TIRF medicines. The focus of the survey included the potential for life-threatening breathing problems that can lead to death, the need for patients to take TIRF medicines if they are opioid-tolerant and strictly follow the directions of the HCP, the caution that patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to an HCP, the requirements that patients should not give TIRF medicines to anyone else even if they have the same symptoms, and that TIRF medicines should be stored in a safe place away from children and properly disposed of. The survey also included questions about whether patients received, read, and understood the product-specific Medication Guide and the PPAF.

In this 36-month survey, all but one of the questions included as part of the key risk messages had a correct response rate of >69%. There was only one question within a key risk message (Question 12 in Key Risk Message 3) that had a component with an understanding rate below the desired threshold of 65% (Component 12b*: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine;* correct response *'True';* correct response rate 36.7%). This concept also scored low in the prescriber KAB survey for this reporting period.

In addition, there was one question included as part of the additional questions about the safe use of TIRF medicines and not included as a key risk message (Question 10; *For which of the following conditions should you use a TIRF medicine?*) that had a component with an understanding rate below the desired threshold of 65% (Component 10e; *Long-lasting painful conditions not caused by cancer*; desired response 'No', response rate 25.3%). For the other 4 components of Question 10, the desired responses were greater than 65% in the 36-month survey. Although the questions are worded differently for the 36-month survey period, this concept also scored low for pharmacists (43.7%). These components were the only low scoring components in all three waves of the patient/caregiver KAB survey.

Question 32 (*Did the doctor or someone in the doctor's office explain the Patient-Prescriber Agreement Form to you?*) (Table 6) shows an increased response (77.7%) compared to the previous two waves which supports that the healthcare professionals are discussing with their patients the safe use and risks of TIRF medicines.

A comparison of the three waves is shown in Table 16.

Table 16. Correct/Desired Response Rate of Low Scoring Questions across the Three Patient/Caregiver KAB Survey Waves.

36-Month Survey Question Number	Questions as Presented in the 36-Month Survey	12-Month Survey Correct/Desired Response Rate (%)	24-Month Survey Correct/Desired Response Rate (%)	36-Month Survey Correct/Desired Response Rate (%)
12	Please answer "True," "False," or "I don't know" for each of the following statements.			
12b	If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine. ***(Correct Response True)***	42.7	34.1	36.7
10[1]	For which of the following conditions should you use a TIRF medicine?			
10e[1]	Long-lasting painful conditions not caused by cancer ***(Desired Response No)***	24.5	21.9	25.3

[1] This was part of Question 9 (9e) in 12-month Patient/Caregiver KAB survey. Question 9 was worded as follows for the 12-month KAB survey: For which of the following conditions should I use a TIRF medicine? Response option for 9e whas "chronic non-cancer pain".

Conclusions

The consistently high level of patient understanding of key risk messages in the 24-month and 36-month surveys indicates that the REMS goals are being met with the tools currently in place. The higher level of understanding in patients who read most or all of the medication guide demonstrates effective communication of the key risk messages, which may also be reinforced by prescribers and pharmacists. The TRIG will evaluate the concepts that have scored low among stakeholders to determine if any action is warranted. The TRIG will continue to work with the FDA to refine, on a continual basis, the steps to mitigate risks associated with TIRF medicines.

Appendix A Patient Survey Protocol

PROTOCOL TITLE:	**Quantitative Testing of Patient/Caregiver Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)** **Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)** **Depomed, Inc.** **Galena Biopharma, Inc.** **Insys Therapeutics** **Mallinckrodt Pharmaceuticals** **Meda Pharmaceuticals** **Mylan, Inc.** **Par Pharmaceutical, Inc.**
VERSION:	**7.0**
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TABLE OF CONTENTS PAGE

	TABLE OF CONTENTS	2
1.	LIST OF ABBREVIATIONS	3
2.	BACKGROUND	4
3.	OBJECTIVES OF THE EVALUATION SURVEY	5
4.	METHODS	5
4.1	Qualitative Research on the Survey	5
4.2	Survey Design	5
4.2.1	Questions and Statements on REMS Goals	6
4.2.2	Additional Questions	9
4.3	Subject Recruitment	9
4.3.1	Measures to Minimize Bias in the Sample	10
5.	STUDY POPULATION	11
5.1.1	Sample Size	11
5.1.2	Inclusion Criteria	11
5.1.3	Exclusion Criteria	12
6.	SURVEY PROCESS	12
6.1	Screening and Survey Administration	12
6.1.1	Telephone	12
6.1.2	Internet	12
6.2	Measures to Minimize Bias in the Survey Process	13
7.	ANALYSIS	13
8.	SAFETY EVENT REPORTING	14
9.	PRIVACY PROTECTION AND CONFIDENTIALITY	14

LIST OF APPENDICES

APPENDIX A	Screening and Main Questionnaire	16
APPENDIX B	SAMPLE Patient Letter of Invitation	41

1. LIST OF ABBREVIATIONS

CATI	Computer-Assisted Telephone Interviewing
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
KAB	Knowledge, Attitudes and Behavior
PBM	Pharmacy Benefits Management
PPAF	Patient-Prescriber Agreement Form
REMS	Risk Evaluation and Mitigation Strategy
SE PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access Program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics, which are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risks of misuse, abuse, addiction, overdose and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients

2. Preventing inappropriate conversion between TIRF medicines

3. Preventing accidental exposure to children and others for whom it was not prescribed

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess patients' and caregivers' knowledge, attitudes, and behavior (KAB) regarding the safe use of TIRF medicines as described in the product-specific Medication Guide. This protocol will describe the administration of the surveys that will be conducted among patients who are treated with TIRF medicines, or their caregivers. Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes and/or educational materials to make them more effective in achieving the goals of the REMS.

The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

3. OBJECTIVES OF THE EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of patients around the following key information and risk messages communicated through the REMS:

1) TIRF medicines can cause life-threatening breathing problems that can lead to death.

2) Patients should not take TIRF medicines if they are not opioid tolerant.

3) TIRF medicines should be taken exactly as prescribed by the healthcare provider.

4) Patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.

5) Patients should not give TIRF medicines to anyone else even if they have the same symptoms.

6) TIRF medicines should be stored in a safe place away from children and properly disposed.

The survey will also include questions about whether patients received, read, and understood the product-specific Medication Guide and Patient-Prescriber Agreement Form (PPAF).

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC), and will be administered by UBC.

4.1 Qualitative Research on the Survey

Qualitative research to test patient comprehension was performed on the patient survey in 2012. Findings were incorporated into the survey prior to implementation of Wave 1.

4.2 Survey Design

This survey will be conducted among a sample of patients or their caregivers who have filled a prescription for a TIRF medicine within the past 4 months prior to survey launch. Respondents who have participated in a previous wave of the TIRF REMS KAB survey will not be eligible to participate in subsequent survey waves.

The survey will be administered using the following modalities:

- Self-administered, online through a secure website

- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

The survey included in Appendix B is written to reflect wording for both methods of survey administration: Internet-based and telephone administration.

4.2.1 Questions and Statements on REMS Goals

The questionnaire is made up of multiple-choice, closed-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and open-ended questions. These will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3. The survey is written to follow principles of health literacy and readability.

Questionnaire items will be presented in several formats:

- Statements or questions asking the respondent to indicate whether the statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use “yes,” “no,” or “I don’t know” as potential response options);

- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and

- Questions allowing for the respondent to provide information about when, where and from whom they obtained a Medication Guide, as well as to list questions they have about information in the Medication Guides.

Questionnaires will be analyzed to determine patient understanding of each key risk message.

For statements or questions that use “true” or “yes” vs. “false” or “no” response options, the desired response for the key risk messages is generally “true” or “yes” indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions are formatted to have the respondent disagree with the statement as written by providing response options of “false” or “no” to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A). For better readability, the patient questions, only, are presented in the key risk messages tables. Caregiver questions are presented in Appendix A.

Key Risk Message 1: TIRF medicines can cause life-threatening breathing problems that can lead to death.		
Question No.	**Question**	**Desired response**
13	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13d	TIRF medicines can cause life-threatening breathing problems that can lead to death.	**TRUE**

Key Risk Message 2: Patients should not take TIRF medicines if they are not opioid tolerant.		
Question No.	**Question**	**Desired response**
11	Please answer True, False, or I don't know for the following statement:	
	TIRF medicines should only be taken by patients who are opioid tolerant.	**TRUE**
12	Please answer True, False, or I don't know for each of the following statements.	
12a	Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	**TRUE**
13	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13b	It is OK for patients to take TIRF medicines for headache pain.	**FALSE**

Key Risk Message 3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12b	If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.	**TRUE**
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13c	TIRF medicines should be taken exactly as prescribed by the doctor.	**TRUE**
17b	It is OK to take TIRF medicines for short-term pain that will go away in a few days.	**FALSE**

Key Risk Message 4: Patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12c	It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	**FALSE**

Key Risk Message 5: Patients should not give TIRF medicines to anyone else even if they have the same symptoms.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12d	A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	**FALSE**
17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17a	Selling or giving away TIRF medicines is against the law.	**TRUE**

Key Risk Message 6: TIRF medicines should be stored in a safe place away from children and properly disposed.		
Question No.	**Question**	**Desired response**
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13a	TIRF medicines should be stored in a safe place out of the reach of children.	**TRUE**
17c	TIRF medicines must be disposed of as described in the specific product's Medication Guide.	**TRUE**
17e	A TIRF medicine can cause an overdose and death in any child who takes it.	**TRUE**
14	What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)	**Get emergency help right away.**

4.2.2 Additional Questions

Questions about the requirements of the TIRF REMS, and receipt and understanding of the Medication Guides and PPAF will be asked after the key risk message questions, and will be followed by the collection of demographic information at the completion of the survey.

4.3 Subject Recruitment

Patients will be recruited through a direct letter program. Patients will be invited through a network of national pharmacies and/or a pharmacy benefits management (PBM) partner,

which will provide a broad demographic coverage and include patients in 49 states. Leveraging one or more of these partners, a list will be created of patients who have filled a prescription for a TIRF medicine within 4 months prior to survey launch (first prescriptions and refills). Patients in this list will be invited to participate in the survey through an invitation letter (Appendix B) mailed directly to the patients on the pharmacy or PBM's letterhead at the corporate level via the United States (US) Postal Service.

The invitation will indicate that participants will receive a $50 gift card for completing the survey. Each invitation will also include a unique code and directions for accessing the survey either via the Internet or by telephone through an interviewer at the Survey Coordinating Center. The unique code will be used to identify the manufacturer of the most recent TIRF prescription that the patient filled.

A sample of patients who have filled a prescription for a TIRF medicine within the 4 months prior to survey launch will be chosen from the pharmacy partner's and/or PBM's database. This sampling approach will be used to create several batches of survey invitations. The overall number of unique patients and the duration of the survey period will dictate the size and number of invitation batches. If the required number of completed surveys is not achieved within a reasonable time frame, a second mailing will be sent to non-respondents from the original batch mailing and initial invitations will be sent to patients in the second batch. If the required number of completed surveys is still not achieved within a reasonable time frame, reminder letters will be sent to the patients in the second batch and initial invitations will be sent to the third batch of patients. If these efforts do not result in the required number of surveys within a reasonable time frame, then a new sample of patients may be selected if available. The intervals for sending reminder invitations to non-responders and for selecting a new sample will be condensed as necessary based on the actual rate of survey accrual relative to the proximity of the target survey close date.

All respondents who complete the survey and who provide their contact information will be mailed a $50 gift card to thank them for their participation. The mailing will include a thank you letter, a copy of the product-specific Medication Guide, and a copy of the correct answers to the key risk message questions.

4.3.1 Measures to Minimize Bias in the Sample

The sample of participating patients will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of patients for participation.

Respondents will be offered online or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the online survey or when calling the Survey

Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

5. STUDY POPULATION

5.1.1 Sample Size

A sample of 300 patients treated with TIRF medicines is proposed for the survey wave. The size of the sample was determined based on both practical and statistical considerations. There is no target comprehension rate specified *a priori*. A sample of 300 completed surveys will allow estimation of the comprehension rate for each key risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval	
5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.2 Inclusion Criteria

The following respondents are eligible to participate in the survey:

- Patients who are 18 years of age or older who have filled a prescription for at least one of the TIRF medicines within 4 months prior to survey launch

- Caregivers 18 years of age or older who care for patients who have filled a TIRF medicine prescription within the past 4 months prior to survey launch and are unable to take the survey for themselves

5.1.3 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Patients who have previously participated in the TIRF REMS KAB survey (this exclusion applies to the second and subsequent waves only)

- Patients or their immediate family members who have ever worked for Anesta LLC, Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc.; Par Pharmaceutical, Inc.; Teva Pharmaceuticals, Ltd.; UBC; McKesson Specialty Care Solutions; RelayHealth; or the FDA.

6. SURVEY PROCESS

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm patient eligibility. The entire survey is expected to take approximately 20 minutes to complete. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, respondents are immediately notified with a thank you message that survey participation has ended. If eligible, respondents are allowed to continue survey participation.

The electronic data capture (EDC) system that is used for both methods of survey administration has been validated and is secure for receiving and storing survey data. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Patient-identifying information will be stored separately from survey data.

6.1.1 Telephone

The telephone survey is facilitated by a trained interviewer from the Survey Coordinating Center using a CATI program. The respondent will be required to provide a unique code to access the survey. Working from a CATI script, the interviewer will read questions or statements to the respondent and enter the responses into the EDC system. Screening and main elements of the questionnaire will be administered sequentially during the same telephone call. Telephone interviewing allows participation of respondents who do not have Internet access, or prefer to complete the survey in this manner.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If respondents select to participate in the survey online, they will be directed to a secured

website and instructed to enter a unique code to access the survey. An Internet survey will be convenient for respondents to participate since they can complete the questionnaire at any convenient time and location during the specified survey time period.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer the survey.

All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. Any free text fields will be grouped into applicable categories. Verbatim text from open-ended questions will be displayed when appropriate. The following will be reported as part of this analysis:

- The number of invitations issued
- The number of reminder letters
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents who completed all questions presented to them
- Description of survey participants, including:
  - Type of respondent (patient/caregiver)
  - Age (patient/caregiver)
  - Gender (respondent)
  - Educational level (respondent)
  - Main language spoken at home (respondent)

  - Ethnicity (respondent)
  - Race (respondent)
  - Geographic region (respondent)

- Data from all respondents who completed all questions presented to them in the survey ("completers") will be analyzed, including:
  - Frequency distribution of responses to each key risk message question.
  - Percent of completers selecting desired response to each question relating to each key risk message and 95% CI.

Measurement of understanding will be computed for each question of the key risk message individually. A secondary analysis will be conducted to determine the number of completers who answered all items correctly for the key risk message. Behavior questions will be summarized on a question-by-question basis and are not included in the analysis by key risk message.

Additional analyses may be performed as needed.

8. SAFETY EVENT REPORTING

The survey will be conducted via the Internet and by telephone. It is possible that a respondent may report an adverse event or other safety event experienced while taking TIRF medicines either in free text fields of the survey or while in conversation with the Survey Coordinating Center. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. The respondent will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact him/her if there are questions about the survey. The Internet-based questionnaires will be monitored for any comments recorded in free text fields. Information on all comments that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE PSP.

9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The EDC system used for data collection encrypts all identifiable information and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail a $50 gift card, a Thank You Letter, a product-specific Medication Guide, and correct survey responses to key risk message questions after the survey is completed. Respondent contact information is also requested in the event a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information. A respondent may be contacted only if clarification or follow-up is needed regarding a possible safety event that was mentioned to the interviewer or recorded in free text fields of the online survey.

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to receive TIRF medicines.

This protocol and survey will be reviewed and approved by a central Institutional Review Board (IRB) before administration of the survey.

APPENDIX A Screening and Main Questionnaire

Survey Legend

- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets. **[PATIENT]** indicates text applicable to a patient when it differs from survey text for caregivers, parents and legal guardians. **[PARENT/CAREGIVER/LEGAL GUARDIAN]** indicates text applicable to parents, caregivers, and legal guardians when it differs from survey text for patients.

- **(INTERVIEWER)** is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by tlelphone only (for example, spontaneous adverse event reporting).

- **[ONLINE]** indicates a question is worded specifically for administering the survey online. **[PHONE]** indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.

- **[BEGIN ONLINE/PHONE SURVEY CONTENT]** and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.

- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

  Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.

- **[RANDOMIZE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as “I don’t know,” “Prefer not to answer” or “None of the above” will always appear at the end of the randomized responses.

- **[GO TO Ax]** (Skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

Survey Legend

- **[FREE TEXT]** indicates to the programmer that one line should be provided for data entry.
- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines).
- **[DROP-DOWN LIST INPUT WITH STATES TABLE]** indicates to the programmer that the response should be a drop-down list containing the states in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

- The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

  Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

  Northeast Region
  - New England Division - ME, NH, VT, MA, RI, CT
  - Middle Atlantic Division - NY, NJ, PA

  Midwest Region
  - East North Central Division - OH, IN, IL, MI, WI
  - West North Central Division - MN, IA, MO, ND, SD, NE, KS

  South Region
  - South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
  - East South Central Division - KY, TN, AL, MS

Survey Legend

- West South Central Division - AR, LA, OK, TX

West

- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV
- Pacific Division WA, OR, CA, AK, HI

- The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

[BEGIN SURVEY CONTENT]

[ONLINE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The survey is being conducted by the makers of Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and the generic versions of any of these brands. These are **T**ransmucosal **I**mmediate **R**elease **F**entanyl medicines, also known as rapid onset opioids (and sometimes called "fast acting fentanyls") or TIRF medicines.

The information collected will help the makers of TIRF medicines know if patients and their caregivers understand important information about taking these medicines. The survey will take about 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. Your answers to the questions or your decision to take part in the survey will not affect your ability to receive or take TIRF medicines.

How We Use Your Information

Your answers to the survey questions will be combined with answers given by other people taking the survey. All answers will be put together and reported in anonymous form to manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 gift card for your time.

Your name and address will be used only to send you the gift card, a Thank You Letter, a product-specific Medication Guide, and a copy of the correct answers to key risk message questions, after you complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your answers.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA (Food and Drug Administration) and a company called (b) (4)., which is the Institutional Review Board (IRB) that looks out for the interest of survey participants. Your choice to allow the manufacturers of TIRF medicines to use your information is entirely voluntary, but necessary to take part in this survey.

If you have questions about your rights as a research participant or related concerns, you may contact the IRB at (b) (4). Be sure to write down this telephone number; it will not be displayed again.

How to Learn More About This Survey

If you have questions about the survey, or have any problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297.

The information in this survey should not take the place of talking with your doctor or health care professional. If you have any questions about your condition or treatment or that of the person you care for, or if you would like more information about TIRF medicines, talk to your doctor, pharmacist, or other health care professional.

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

[PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The survey is being conducted by the makers of Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and the generic versions of any of these brands. These are Transmucosal Immediate Release Fentanyl medicines, also known as rapid onset opioids **(INTERVIEWER: Please pause briefly)** (and sometimes called "fast acting fentanyls") or TIRF medicines.

(INTERVIEWER: Pronounce "TIRF," then spell out T-I-R-F).

The information collected will help the makers of TIRF medicines know if patients and their caregivers understand important information about taking these medicines. The survey will take about 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. Your answers to the questions or your decision to take part in the survey will not affect your ability to receive or take TIRF medicines.

Now I would like to tell you about how your contact information will be used.

Your answers to the survey questions will be combined with answers given by other people taking the survey. All answers will be put together and reported in anonymous form to manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 gift card for your time.

Your name and address will be used only to send you the gift card, a Thank You Letter, a product-specific Medication Guide, and a copy of the correct answers to key risk message questions, after you complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your answers.

Now I would like to tell you about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA (Food and Drug Administration) and a company called (b) (4)., which is the Institutional Review Board (IRB) that looks out for the interest of survey participants. Your choice to allow the manufacturers of TIRF medicines to use your information is entirely voluntary, but necessary to take part in this survey.

If you have questions about your rights as a research participant or related concerns, you may contact the IRB at (b) (4)

The information in this survey should not take the place of talking with your doctor or health care professional. If you have any questions about your condition or treatment or that of the person you care for, or if you would like more information about TIRF medicines, talk to your doctor, pharmacist, or other health care professional.

Please feel free to ask me to repeat any questions or statements as we go through the survey.

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END PHONE PREAMBLE 1]

1. Do you agree to take part in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Within the last 4 months, have you filled a prescription for yourself for a transmucosal immediate release fentanyl medicine (known as "TIRF medicines")? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of any of these brands.

   - ○ Yes **[GO TO Q4]**
   - ○ No
   - ○ I don't know

3. Are you a caregiver for someone who has filled a prescription for a TIRF medicine within the last 4 months? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and the generic versions of any of these brands.

   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

4. **[PATIENT]** For which TIRF medicines have you filled a prescription in the last 4 months? Please select all that apply.

[CAREGIVER] For which TIRF medicines has the person you care for filled a prescription in the last 4 months? Please select all that apply.

- □ Abstral
- □ Actiq, including generic versions of Actiq
- □ Fentora
- □ Lazanda
- □ Onsolis
- □ Subsys
- □ Other
- □ I don't know **[CLEAR ALL OTHER SELECTIONS]**

5. Have you ever taken part in a survey about a TIRF medicine before?

- ○ Yes **[TERMINATE]**
- ○ No
- ○ I don't know **[TERMINATE]**

6. Which of the following groups best describes your age?

- ○ Under 18 **[TERMINATE]**
- ○ 18 – 29
- ○ 30 – 39
- ○ 40 – 49
- ○ 50 – 59
- ○ 60 – 69
- ○ 70 or older
- ○ Prefer not to answer **[TERMINATE]**

7. **[CAREGIVER ONLY]** Which of the following groups best describes the patient's age?

- ○ Under 16
- ○ 16 – 29
- ○ 30 – 39
- ○ 40 – 49
- ○ 50 – 59
- ○ 60 – 69
- ○ 70 or older
- ○ Prefer not to answer **[TERMINATE]**

8. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

- ☐ Anesta LLC **[TERMINATE]**
- ☐ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**
- ☐ Depomed, Inc. **[TERMINATE]**
- ☐ Galena Biopharma, Inc. **[TERMINATE]**
- ☐ Insys Therapeutics **[TERMINATE]**
- ☐ Mallinckrodt Pharmaceuticals **[TERMINATE]**
- ☐ McKesson Specialty Care Solutions **[TERMINATE]**
- ☐ Meda Pharmaceuticals **[TERMINATE]**
- ☐ Mylan, Inc. **[TERMINATE]**
- ☐ Par Pharmaceutical, Inc. **[TERMINATE]**
- ☐ RelayHealth**[TERMINATE]**
- ☐ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- ☐ United BioSource Corporation **[TERMINATE]**
- ☐ FDA (Food and Drug Administration) **[TERMINATE]**
- ☐ No **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- ☐ I don't know **[TERMINATE]**

[PREAMBLE 2]

[PATIENT]Please answer the following questions based on information about the TIRF medicine that was most recently prescribed for you. TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands. Please think of the information that you read or that was provided to you by a doctor, nurse, or other healthcare professional. If you don't know the answers to any of the following questions please respond "I don't know" instead of guessing the correct responses.

[CAREGIVER]Please answer the following questions based on information about the TIRF medicine that was most recently prescribed for the patient. TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands. Please think of the information that you read or that was provided to you or to the patient by a doctor, nurse, or other healthcare professional. If you don't know the answers to any of the following questions please respond "I don't know" instead of guessing the correct responses.

9. **[PATIENT]** Did the doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed for you? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands.

[CAREGIVER] Did the doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed to the patient? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands.

- ○ Yes
- ○ No
- ○ I don't know

10. **[PATIENT]** For which of the following conditions should you use a TIRF medicine?

[CAREGIVER] For which of the following conditions should the person you take care of use a TIRF medicine?

	[RANDOMIZE LIST]	**Yes**	**No**	**I don't know**
10a.	Headache or migraine pain	○	○	○
10b.	Breakthrough pain from cancer	○	○	○
10c.	Dental pain	○	○	○
10d.	Pain after surgery	○	○	○
10e.	Long-lasting painful conditions not caused by cancer	○	○	○

11. Please answer True, False, or I don't know for the following statement:

TIRF medicines should only be taken by patients who are opioid tolerant.

- ○ True
- ○ False
- ○ I don't know

12. Please answer True, False, or I don't know for each of the following statements.

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
12a.	Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	○	○	○
12b.	If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.	○	○	○
12c.	It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	○	○	○
12d.	A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	○	○	○

13. **[PATIENT]** Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.

[CAREGIVER] Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for the patient.

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
13a.	TIRF medicines should be stored in a safe place out of the reach of children.	○	○	○
13b.	It is OK for patients to take TIRF medicines for headache pain.	○	○	○
13c.	TIRF medicines should be taken exactly as prescribed by the doctor.	○	○	○
13d.	TIRF medicines can cause life-threatening breathing problems that can lead to death.	○	○	○

14. What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)

[RANDOMIZE LIST]

- ○ Wait an hour and see if the person is OK.
- ○ Get emergency help right away.
- ○ Do nothing.
- ○ I don't know.

15. **[PATIENT]** Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for you?

[CAREGIVER] Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for the patient?

- o Yes
- o No
- o I don't know

16. **[PATIENT]** Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for you?

[CAREGIVER] Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for the patient?

- o Yes
- o No
- o I don't know

17. **[PATIENT]** Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.

[CAREGIVER] Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for the patient.

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
17a.	Selling or giving away TIRF medicines is against the law.	○	○	○
17b.	It is OK to take TIRF medicines for short-term pain that will go away in a few days.	○	○	○
17c.	TIRF medicines must be disposed of as described in the specific product's Medication Guide.	○	○	○
17d.	TIRF medicines are only available to patients through a pharmacy enrolled in a special program (called the TIRF REMS Access Program).	○	○	○
17e.	A TIRF medicine can cause an overdose and death in any child who takes it.	○	○	○

[PREAMBLE 3]

[PATIENT] The next set of questions is about the Medication Guide for the TIRF medicine that was most recently prescribed for you.

[CAREGIVER] The next set of questions is about the Medication Guide for the TIRF medicine that was most recently prescribed for the patient.

[BOTH] A Medication Guide is a paper handout that contains important information about the risks associated with the use of a TIRF medicine and how to use it safely. Medication Guides always include the title "Medication Guide" followed by the name of the medicine and its pronunciation. The Medication Guide usually has a section titled "What is the most important information I should know?" The Medication Guide is in a question-and-answer format and may be given to you by your pharmacist, doctor, or other healthcare professional.

18. **[PATIENT]** Have you ever received a Medication Guide for the TIRF medicine that was prescribed for you?

[CAREGIVER] Have you or the patient ever received a Medication Guide for the TIRF medicine that was prescribed for the patient?

- ○ Yes
- ○ No **[GO TO PREAMBLE 4]**
- ○ I don't know **[GO TO PREAMBLE 4]**

19. **[PATIENT]** Did you receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?

[CAREGIVER] Did you or the patient receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?

- ○ Yes
- ○ No **[GO TO Q21]**
- ○ I don't know **[GO TO Q21]**

20. **[PATIENT]** When was the Medication Guide given to you? Please select all that apply.

[CAREGIVER] When was the Medication Guide given to you or the patient? Please select all that apply.

- □ At the first appointment with the doctor who prescribed the TIRF medicine
- □ At the last appointment with the doctor who prescribed the TIRF medicine
- □ I don't remember **[CLEAR ALL OTHER SELECTIONS]**

21. **[PATIENT]** Did you receive the Medication Guide for the TIRF medicine from the pharmacy?

[CAREGIVER] Did you or the patient receive the Medication Guide for the TIRF medicine from the pharmacy?

- ○ Yes
- ○ No **[GO TO Q23]**
- ○ I don't know **[GO TO Q23]**

22. **[PATIENT]** How frequently do you receive a Medication Guide for the TIRF medicine at the pharmacy?

[CAREGIVER] How frequently do you or the patient receive a Medication Guide for the TIRF medicine at the pharmacy?

- ○ Only with the first filled prescription
- ○ Each time a prescription is filled
- ○ Other (please specify): _____
- ○ I don't know

23. Did you read the Medication Guide?

- ○ Yes
- ○ No **[GO TO Q26]**
- ○ I don't know **[GO TO Q26]**

24. How much did you read?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ I don't know

25. How much of the Medication Guide did you understand?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ None of it
- ○ I don't know

26. Did someone offer to explain the Medication Guide to you?

- ○ Yes
- ○ No **[GO TO Q30]**
- ○ I don't know **[GO TO Q30]**

27. Who offered to explain the Medication Guide to you? Please select all that apply.

- □ The doctor or another healthcare professional in the doctor's office
- □ The pharmacist where the TIRF medicine prescription was filled
- □ Someone else (specify the type of person but not his/her name)

[FREE TEXT]

28. Did you accept the offer to have the Medication Guide explained to you?

- ○ Yes
- ○ No **[GO TO Q30]**
- ○ I don't know **[GO TO Q30]**

29. How much of the explanation did you understand?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ None of it
- ○ I don't know

30. Did you or do you have any questions about the information in the Medication Guide?

- ○ Yes
- ○ No **[GO TO PREAMBLE 4]**
- ○ I don't know **[GO TO PREAMBLE 4]**

31. What are your questions? **[MULTILINE INPUT]**

[PREAMBLE 4]

The next set of questions is about the Patient-Prescriber Agreement Form for TIRF medicines. As a reminder, TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of any of these brands. The Patient-Prescriber Agreement is a form that is signed by the doctor and the patient or their caregiver. This form may also be referred to as the Prescriber-Patient Agreement.

[END PREAMBLE 4]

32. Did the doctor or someone in the doctor's office explain the Patient-Prescriber Agreement Form to you?

- ○ Yes
- ○ No **[GO TO Q34]**
- ○ I don't know **[GO TO Q34]**

33. How much of the explanation did you understand?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ None of it
- ○ I don't know

34. **[PATIENT]** Did you sign a Patient-Prescriber Agreement Form?

[CAREGIVER] Did you or the person you are caring for sign a Patient-Prescriber Agreement Form?

- ○ Yes
- ○ No **[GO TO DEMOGRAPHICS PREAMBLE]**
- ○ I don't know **[GO TO DEMOGRAPHICS PREAMBLE]**

35. Did the doctor or someone in the doctor's office give you a copy of the signed Patient-Prescriber Agreement Form?

- ○ Yes
- ○ No
- ○ I don't know

[DEMOGRAPHICS PREAMBLE]

There are just a few more questions to help us combine your answers with other answers we have received.

36. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

37. What is the highest level of education you have completed?

- ○ Less than high school
- ○ Some high school
- ○ High school graduate/GED
- ○ Some college/Associate's degree
- ○ Bachelor's degree
- ○ Master's degree
- ○ Professional or Doctoral degree
- ○ Prefer not to answer

38. What is the main language you speak at home?

- ○ English
- ○ French
- ○ Spanish
- ○ Portuguese
- ○ Italian
- ○ German
- ○ Chinese
- ○ Japanese
- ○ Korean
- ○ Other
- ○ Prefer not to answer

39. Are you Hispanic or Latino?

- ○ Yes
- ○ No
- ○ Prefer not to answer

40. For informational purposes only, which of the following U.S. census categories best describes your race?

- ○ American Indian or Alaska Native
- ○ Asian (origins of Far East, Southeast Asia or the Indian subcontinent)
- ○ Black or African American
- ○ Native Hawaiian or Other Pacific Islander
- ○ White
- ○ Two or more races
- ○ Other
- ○ Prefer not to answer

41. In which state do you live?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" AT END]

[PHONE ONLY: ADVERSE EVENT/PRODUCT COMPLAINT]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- ○ Yes
- ○ No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[CLOSING 1]

You are eligible to receive a $50 gift card for your time completing the survey. In order to receive the gift card, we need to collect your name and address so that we can mail it to you. If you do not provide your name and address you will not receive the gift card for your time taking the survey.

Do you agree to give us your name and mailing address so we can send your payment?

- ○ Yes
- ○ No **[SKIP TO CLOSING 2]**

FIRST NAME: [**FREE TEXT]**

LAST NAME: [**FREE TEXT]**

ADDRESS: **[MULTILINE INPUT]**

CITY: [**FREE TEXT]**

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: **[5 NUMERIC CHARACTERS ONLY]**

[CLOSING 2]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

Do you want to provide your telephone number?

○ Yes

○ No **[SKIP TO CLOSING 3]**

Telephone: **[10-DIGIT NUMERIC CHARACTERS]**

[END CLOSING 2]

[CLOSING 3]

This is the end of the survey. If you have questions about the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Thank you again for your help.

[END OF SURVEY CONTENT]

APPENDIX B SAMPLE Patient Letter of Invitation

[PAT_FIRST_NAME] [PAT_LAST_NAME
[CURR_DATE]
[PAT_STREET_ADDR]
[PAT_CITY], [PAT_STATE] [PAT_ZIP]

Dear [PAT_FULL_NAME]:

Thank you for choosing [pharmacy partner or PBM name] for your prescription needs. The purpose of this letter is to inform you about a voluntary research survey being conducted by [COMPANY], the maker of [BRAND_GENERIC]. The survey is part of an FDA requirement to find out if patients and/or their caregivers understand important safety information about [BRAND] and other medicines like it. The first 300 people who complete this 20-minute survey and provide their contact information will receive a $50 [pharmacy partner or PBM name] gift card from [COMPANY] to thank them for their time.

You may be eligible to take part if you have taken [BRAND] and are 18 years of age or older. If you are unable to take the survey yourself, a caregiver who is 18 or older may be eligible to take the survey for you. The survey asks questions about the type of information you received about [BRAND] and where you get your medical information.

If you are interested in participating and to find out if you are eligible:

- Go to www.TIRFREMSsurvey.com any time or
- Call 877-379-3297, 8 a.m. to 8 p.m. Eastern Time, Monday through Friday

Please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**.

It is recommended that you take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.

(over, please)

You are not required to take part in this survey. If you choose to take part, please be assured that your contact information and your individual responses will be kept strictly confidential. You will not be asked to identify yourself to participate in the survey. However, if you wish to receive the $50 gift card from [COMPANY], you must provide your name and contact information for delivery. Your answers to the survey questions will be combined with answers given by others, and your name will not be used in any written report or publication. Neither taking the survey nor your answers to the questions will affect your ability to receive or take [BRAND].

Sincerely,

[Pharmacy partner or PBM name]

[COMPANY] funded the cost of the gift card, the cost of mailing this letter and paid a fee to [pharmacy partner or PBM name]. The research study is not being conducted by [pharmacy partner or PBM name]. No information that can identify you, your medication, or your health condition will be provided by [pharmacy partner or PBM name] to [COMPANY]. This letter provides information about a drug prescribed by your doctor and is not a recommendation by [pharmacy partner or PBM name] to use a particular drug for your condition. Call [pharmacy partner or PBM name] toll free at xxx-xxx-xxxx if you do not wish to continue receiving mailings about [BRAND] from [pharmacy partner or PBM name].

Appendix B Patient Survey Listings and Sub-group Analyses Tables

TABLE 6.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 1: TIRF MEDICINES CAN CAUSE LIFE-THREATENING BREATHING PROBLEMS THAT CAN LEAD TO DEATH.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, QUESTION 23, AND QUESTION 24):

- **S-1a - Respondents who received the Medication Guide and read at least most of it.**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know."**

Question	S-1a Read most of Med Guide N=193		S-1b Read some or none of Med Guide N=36	
	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.				
True [1]	180	93.3 (88.8, 96.4)	29	80.6 (64.0, 91.8)
False	1	0.5	0	0.0
I don't know	12	6.2	7	19.4

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, QUESTION 23, AND QUESTION 24):

- **S-1a - Respondents who received the Medication Guide and read at least most of it.**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know."**

Question	S-1a Read most of Med Guide N=193		S-1b Read some or none of Med Guide N=36	
	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statement:				
TIRF medicines should only be taken by patients who are opioid tolerant.				
True [1]	170	88.1 (82.7, 92.3)	25	69.4 (51.9, 83.7)
False	5	2.6	1	2.8
I don't know	18	9.3	10	27.8
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.				
True [1]	163	84.5 (78.6, 89.3)	24	66.7 (49.0, 81.4)
False	14	7.3	5	13.9
I don't know	16	8.3	7	19.4

Question	S-1a Read most of Med Guide N=193		S-1b Read some or none of Med Guide N=36	
	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13b: It is OK for patients to take TIRF medicines for headache pain.				
False [1]	141	73.1 (66.2, 79.2)	18	50.0 (32.9, 67.1)
True	12	6.2	4	11.1
I don't know	40	20.7	14	38.9

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, QUESTION 23, AND QUESTION 24):

- **S-1a - Respondents who received the Medication Guide and read at least most of it.**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know."**

Demonstrated Understanding	S-1a Read most of Med Guide N=193		S-1b Read some or none of Med Guide N=36	
	N	%	N	%
0 correct responses	5	2.6	5	13.9
1 correct response	15	7.8	6	16.7
2 correct responses	60	31.1	14	38.9
3 correct responses	113	58.5	11	30.6
Average number of correct responses	2.5 (2.3, 3.0) [1]		1.9 (1.5, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3 IN ELIGIBLE AND COMPLETE RESPONDENTS

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, QUESTION 23, AND QUESTION 24):

- **S-1a - Respondents who received the Medication Guide and read at least most of it.**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know."**

Question	S-1a Read most of Med Guide N=193		S-1b Read some or none of Med Guide N=36	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.				
True [1]	79	40.9 (33.9, 48.2)	5	13.9 (4.7, 29.5)
False	46	23.8	12	33.3
I don't know	68	35.2	19	52.8
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13c: TIRF medicines should be taken exactly as prescribed by the doctor.				
True [1]	193	100.0 (98.1, 100.0)	34	94.4 (81.3, 99.3)
False	0	0.0	2	5.6
I don't know	0	0.0	0	0.0

Question	S-1a Read most of Med Guide N=193		S-1b Read some or none of Med Guide N=36	
	N	% (95% CI)	N	% (95% CI)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.				
False [1]	168	87.0 (81.5, 91.4)	22	61.1 (43.5, 76.9)
True	10	5.2	2	5.6
I don't know	15	7.8	12	33.3

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, QUESTION 23, AND QUESTION 24):

- **S-1a - Respondents who received the Medication Guide and read at least most of it.**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know."**

Demonstrated Understanding	S-1a Read most of Med Guide N=193		S-1b Read some or none of Med Guide N=36	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	16	8.3	14	38.9
2 correct responses	107	55.4	19	52.8
3 correct responses	70	36.3	3	8.3
Average number of correct responses	2.3 (2.1, 3.0) [1]		1.7 (1.3, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 9.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4 IN ELIGIBLE AND COMPLETE RESPONDENTS

RISK MESSAGE 4: PATIENTS SHOULD NOT SWITCH FROM A TIRF MEDICINE TO ANOTHER MEDICINE THAT CONTAINS FENTANYL WITHOUT TALKING TO A HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, QUESTION 23, AND QUESTION 24):

- **S-1a - Respondents who received the Medication Guide and read at least most of it.**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know."**

Question	S-1a Read most of Med Guide N=193		S-1b Read some or none of Med Guide N=36	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.				
False [1]	188	97.4 (94.1, 99.2)	34	94.4 (81.3, 99.3)
True	2	1.0	0	0.0
I don't know	3	1.6	2	5.6

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 10.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, QUESTION 23, AND QUESTION 24):

- **S-1a - Respondents who received the Medication Guide and read at least most of it.**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know."**

Question	S-1a Read most of Med Guide N=193		S-1b Read some or none of Med Guide N=36	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.				
False [1]	191	99.0 (96.3, 99.9)	36	100.0 (90.3, 100.0)
True	1	0.5	0	0.0
I don't know	1	0.5	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17a: Selling or giving away TIRF medicines is against the law.				
True [1]	192	99.5 (97.1, 100.0)	35	97.2 (85.5, 99.9)
False	1	0.5	0	0.0
I don't know	0	0.0	1	2.8

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 10.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, QUESTION 23, AND QUESTION 24):

- **S-1a - Respondents who received the Medication Guide and read at least most of it.**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know."**

Demonstrated Understanding	S-1a Read most of Med Guide N=193		S-1b Read some or none of Med Guide N=36	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	3	1.6	1	2.8
2 correct responses	190	98.4	35	97.2
Average number of correct responses	2.0 (1.8, 2.0) [1]		2.0 (1.6, 2.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 11.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, QUESTION 23, AND QUESTION 24):

- **S-1a - Respondents who received the Medication Guide and read at least most of it.**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know."**

Question	S-1a Read most of Med Guide N=193		S-1b Read some or none of Med Guide N=36	
	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13a: TIRF medicines should be stored in a safe place out of the reach of children.				
True [1]	191	99.0 (96.3, 99.9)	36	100.0 (90.3, 100.0)
False	1	0.5	0	0.0
I don't know	1	0.5	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.				
True [1]	185	95.9 (92.0, 98.2)	30	83.3 (67.2, 93.6)
False	0	0.0	0	0.0
I don't know	8	4.1	6	16.7

Question	S-1a Read most of Med Guide N=193		S-1b Read some or none of Med Guide N=36	
	N	% (95% CI)	N	% (95% CI)
17e: A TIRF medicine can cause an overdose and death in any child who takes it.				
True [1]	176	91.2 (86.3, 94.8)	31	86.1 (70.5, 95.3)
False	1	0.5	1	2.8
I don't know	16	8.3	4	11.1
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)				
Get emergency help right away. [1]	173	89.6 (84.4, 93.6)	29	80.6 (64.0, 91.8)
Do nothing.	0	0.0	0	0.0
Wait an hour and see if the person is OK.	5	2.6	2	5.6
I don't know.	15	7.8	5	13.9

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 11.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, QUESTION 23, AND QUESTION 24):

- **S-1a - Respondents who received the Medication Guide and read at least most of it.**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know."**

Demonstrated Understanding	S-1a Read most of Med Guide N=193		S-1b Read some or none of Med Guide N=36	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	1	0.5	1	2.8
2 correct responses	5	2.6	4	11.1
3 correct responses	34	17.6	7	19.4
4 correct responses	153	79.3	24	66.7
Average number of correct responses	3.8 (3.5, 4.0) [1]		3.5 (3.0, 4.0) [1]	

[1] One-sided 95% confidence interval using the normal approximation to the Poisson distribution.

TABLE 6.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 1: TIRF MEDICINES CAN CAUSE LIFE-THREATENING BREATHING PROBLEMS THAT CAN LEAD TO DEATH.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 18, 23, AND 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Question	S-2a Understood All or Most N=184		S-2b Understood Some N=25		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.								
True [1]	170	92.4 (87.6, 95.8)	22	88.0 (68.8, 97.5)	0	-	17	85.0 (62.1, 96.8)
False	1	0.5	0	0.0	0	-	0	0.0
I don't know	13	7.1	3	12.0	0	-	3	15.0

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 18, 23, AND 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Question	S-2a Understood All or Most N=184		S-2b Understood Some N=25		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statement:								
TIRF medicines should only be taken by patients who are opioid tolerant.								
True [1]	164	89.1 (83.7, 93.2)	17	68.0 (46.5, 85.1)	0	-	14	70.0 (45.7, 88.1)
False	2	1.1	3	12.0	0	-	1	5.0
I don't know	18	9.8	5	20.0	0	-	5	25.0

Question	S-2a Understood All or Most N=184		S-2b Understood Some N=25		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.								
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.								
True [1]	156	84.8 (78.8, 89.6)	16	64.0 (42.5, 82.0)	0	-	15	75.0 (50.9, 91.3)
False	13	7.1	3	12.0	0	-	3	15.0
I don't know	15	8.2	6	24.0	0	-	2	10.0
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13b: It is OK for patients to take TIRF medicines for headache pain.								
False [1]	134	72.8 (65.8, 79.1)	15	60.0 (38.7, 78.9)	0	-	10	50.0 (27.2, 72.8)
True	14	7.6	0	0.0	0	-	2	10.0
I don't know	36	19.6	10	40.0	0	-	8	40.0

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 18, 23, AND 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Demonstrated Understanding	S-2a Understood All or Most N=184		S-2b Understood Some N=25		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=20	
	N	%	N	%	N	%	N	%
0 correct responses	5	2.7	2	8.0	0	-	3	15.0
1 correct response	13	7.1	6	24.0	0	-	2	10.0
2 correct responses	57	31.0	9	36.0	0	-	8	40.0
3 correct responses	109	59.2	8	32.0	0	-	7	35.0
Average number of correct responses	2.5 (2.3, 3.0) [1]		1.9 (1.5, 3.0) [1]		-		2.0 (1.4, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3 IN ELIGIBLE AND COMPLETE RESPONDENTS

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 18, 23, AND 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Question	S-2a Understood All or Most N=184		S-2b Understood Some N=25		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.								
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.								
True [1]	74	40.2 (33.1, 47.7)	7	28.0 (12.1, 49.4)	0	-	3	15.0 (3.2, 37.9)
False	48	26.1	3	12.0	0	-	7	35.0
I don't know	62	33.7	15	60.0	0	-	10	50.0
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								

Question	S-2a Understood All or Most N=184		S-2b Understood Some N=25		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
13c: TIRF medicines should be taken exactly as prescribed by the doctor.								
True [1]	184	100.0 (98.0, 100.0)	25	100.0 (86.3, 100.0)	0	-	18	90.0 (68.3, 98.8)
False	0	0.0	0	0.0	0	-	2	10.0
I don't know	0	0.0	0	0.0	0	-	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.								
False [1]	158	85.9 (80.0, 90.6)	19	76.0 (54.9, 90.6)	0	-	13	65.0 (40.8, 84.6)
True	10	5.4	0	0.0	0	-	2	10.0
I don't know	16	8.7	6	24.0	0	-	5	25.0

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 18, 23, AND 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Demonstrated Understanding	S-2a Understood All or Most N=184		S-2b Understood Some N=25		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=20	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	-	0	0.0
1 correct response	17	9.2	6	24.0	0	-	7	35.0
2 correct responses	102	55.4	12	48.0	0	-	12	60.0
3 correct responses	65	35.3	7	28.0	0	-	1	5.0
Average number of correct responses	2.3 (2.1, 3.0) [1]		2.0 (1.6, 3.0) [1]		-		1.7 (1.2, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 9.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4 IN ELIGIBLE AND COMPLETE RESPONDENTS

RISK MESSAGE 4: PATIENTS SHOULD NOT SWITCH FROM A TIRF MEDICINE TO ANOTHER MEDICINE THAT CONTAINS FENTANYL WITHOUT TALKING TO A HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 18, 23, AND 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Question	S-2a Understood All or Most N=184		S-2b Understood Some N=25		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.								
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.								
False [1]	178	96.7 (93.0, 98.8)	25	100.0 (86.3, 100.0)	0	-	19	95.0 (75.1, 99.9)
True	2	1.1	0	0.0	0	-	0	0.0
I don't know	4	2.2	0	0.0	0	-	1	5.0

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 10.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 18, 23, AND 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Question	S-2a Understood All or Most N=184		S-2b Understood Some N=25		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.								
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.								
False [1]	182	98.9 (96.1, 99.9)	25	100.0 (86.3, 100.0)	0	-	20	100.0 (83.2, 100.0)
True	1	0.5	0	0.0	0	-	0	0.0
I don't know	1	0.5	0	0.0	0	-	0	0.0

Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17a: Selling or giving away TIRF medicines is against the law.								
True [1]	184	100.0 (98.0, 100.0)	24	96.0 (79.6, 99.9)	0	-	19	95.0 (75.1, 99.9)
False	0	0.0	1	4.0	0	-	0	0.0
I don't know	0	0.0	0	0.0	0	-	1	5.0

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 10.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 18, 23, AND 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Demonstrated Understanding	S-2a Understood All or Most N=184		S-2b Understood Some N=25		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=20	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	-	0	0.0
1 correct response	2	1.1	1	4.0	0	-	1	5.0
2 correct responses	182	98.9	24	96.0	0	-	19	95.0
Average number of correct responses	2.0 (1.8, 2.0) [1]		2.0 (1.5, 2.0) [1]		-		2.0 (1.4, 2.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 11.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 18, 23, AND 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Question	S-2a Understood All or Most N=184		S-2b Understood Some N=25		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13a: TIRF medicines should be stored in a safe place out of the reach of children.								
True [1]	182	98.9 (96.1, 99.9)	25	100.0 (86.3, 100.0)	0	-	20	100.0 (83.2, 100.0)
False	1	0.5	0	0.0	0	-	0	0.0
I don't know	1	0.5	0	0.0	0	-	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.								
True [1]	177	96.2 (92.3, 98.5)	22	88.0 (68.8, 97.5)	0	-	16	80.0 (56.3, 94.3)
False	0	0.0	0	0.0	0	-	0	0.0
I don't know	7	3.8	3	12.0	0	-	4	20.0

Question	S-2a Understood All or Most N=184		S-2b Understood Some N=25		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
17e: A TIRF medicine can cause an overdose and death in any child who takes it.								
True [1]	168	91.3 (86.3, 94.9)	20	80.0 (59.3, 93.2)	0	-	19	95.0 (75.1, 99.9)
False	2	1.1	0	0.0	0	-	0	0.0
I don't know	14	7.6	5	20.0	0	-	1	5.0
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)								
Get emergency help right away. [1]	163	88.6 (83.1, 92.8)	22	88.0 (68.8, 97.5)	0	-	17	85.0 (62.1, 96.8)
Do nothing.	0	0.0	0	0.0	0	-	0	0.0
Wait an hour and see if the person is OK.	4	2.2	2	8.0	0	-	1	5.0
I don't know.	17	9.2	1	4.0	0	-	2	10.0

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 11.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 18, 23, AND 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Demonstrated Understanding	S-2a Understood All or Most N=184		S-2b Understood Some N=25		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=20	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	-	0	0.0
1 correct response	1	0.5	0	0.0	0	-	1	5.0
2 correct responses	7	3.8	1	4.0	0	-	1	5.0
3 correct responses	29	15.8	9	36.0	0	-	3	15.0
4 correct responses	147	79.9	15	60.0	0	-	15	75.0
Average number of correct responses	3.8 (3.5, 4.0) [1]		3.6 (2.9, 4.0) [1]		-		3.6 (2.9, 4.0) [1]	

[1] One-sided 95% confidence interval using the normal approximation to the Poisson distribution.

TABLE 6.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 1: TIRF MEDICINES CAN CAUSE LIFE-THREATENING BREATHING PROBLEMS THAT CAN LEAD TO DEATH.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to <20 min**
- **S-3c - ≥ 20 min**

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=81		S-3c ≥ 20 min N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.						
True [1]	44	88.0 (75.7, 95.5)	75	92.6 (84.6, 97.2)	20	100.0 (83.2, 100.0)
False	0	0.0	0	0.0	0	0.0
I don't know	6	12.0	6	7.4	0	0.0

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to <20 min**
- **S-3c - ≥ 20 min**

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=81		S-3c ≥20 min N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statement:						
TIRF medicines should only be taken by patients who are opioid tolerant.						
True [1]	42	84.0 (70.9, 92.8)	74	91.4 (83.0, 96.5)	18	90.0 (68.3, 98.8)
False	1	2.0	2	2.5	0	0.0
I don't know	7	14.0	5	6.2	2	10.0
Question 12: Please answer True, False, or I don't know for each of the following statements.						
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.						
True [1]	40	80.0 (66.3, 90.0)	71	87.7 (78.5, 93.9)	16	80.0 (56.3, 94.3)
False	7	14.0	4	4.9	2	10.0
I don't know	3	6.0	6	7.4	2	10.0

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=81		S-3c ≥20 min N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13b: It is OK for patients to take TIRF medicines for headache pain.						
False [1]	34	68.0 (53.3, 80.5)	58	71.6 (60.5, 81.1)	17	85.0 (62.1, 96.8)
True	4	8.0	6	7.4	0	0.0
I don't know	12	24.0	17	21.0	3	15.0

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to <20 min**
- **S-3c - ≥20 min**

Demonstrated Understanding	S-3a <10 min N=50		S-3b 10 to <20 min N=81		S-3c ≥ 20 min N=20	
	N	%	N	%	N	%
0 correct responses	2	4.0	3	3.7	0	0.0
1 correct response	4	8.0	6	7.4	3	15.0
2 correct responses	20	40.0	19	23.5	3	15.0
3 correct responses	24	48.0	53	65.4	14	70.0
Average number of correct responses	2.3 (2.0, 3.0) [1]		2.5 (2.2, 3.0) [1]		2.6 (2.0, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3 IN ELIGIBLE AND COMPLETE RESPONDENTS

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to <20 min**
- **S-3c - ≥20 min**

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=81		S-3c ≥20 min N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.						
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.						
True [1]	23	46.0 (31.8, 60.7)	33	40.7 (29.9, 52.2)	10	50.0 (27.2, 72.8)
False	11	22.0	21	25.9	4	20.0
I don't know	16	32.0	27	33.3	6	30.0
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13c: TIRF medicines should be taken exactly as prescribed by the doctor.						
True [1]	50	100.0 (92.9, 100.0)	80	98.8 (93.3, 100.0)	20	100.0 (83.2, 100.0)
False	0	0.0	1	1.2	0	0.0
I don't know	0	0.0	0	0.0	0	0.0

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=81		S-3c ≥20 min N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.						
False [1]	41	82.0 (68.6, 91.4)	69	85.2 (75.6, 92.1)	19	95.0 (75.1, 99.9)
True	3	6.0	5	6.2	1	5.0
I don't know	6	12.0	7	8.6	0	0.0

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to<20 min**
- **S-3c - ≥20 min**

Demonstrated Understanding	S-3a <10 min N=50		S-3b 10 to <20 min N=81		S-3c ≥20 min N=20	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	7	14.0	9	11.1	0	0.0
2 correct responses	22	44.0	43	53.1	11	55.0
3 correct responses	21	42.0	29	35.8	9	45.0
Average number of correct responses	2.3 (1.9, 3.0) [1]		2.2 (2.0, 3.0) [1]		2.5 (1.9, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 9.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4 IN ELIGIBLE AND COMPLETE RESPONDENTS

RISK MESSAGE 4: PATIENTS SHOULD NOT SWITCH FROM A TIRF MEDICINE TO ANOTHER MEDICINE THAT CONTAINS FENTANYL WITHOUT TALKING TO A HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to<20 min**
- **S-3c - ≥20 min**

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=81		S-3c ≥20 min N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.						
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.						
False [1]	50	100.0 (92.9, 100.0)	77	95.1 (87.8, 98.6)	20	100.0 (83.2, 100.0)
True	0	0.0	2	2.5	0	0.0
I don't know	0	0.0	2	2.5	0	0.0

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 10.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to<20 min**
- **S-3c - ≥20 min**

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=81		S-3c ≥20 min N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.						
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.						
False [1]	49	98.0 (89.4, 99.9)	81	100.0 (95.5, 100.0)	20	100.0 (83.2, 100.0)
True	1	2.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17a: Selling or giving away TIRF medicines is against the law.						
True [1]	50	100.0 (92.9, 100.0)	80	98.8 (93.3, 100.0)	20	100.0 (83.2, 100.0)
False	0	0.0	1	1.2	0	0.0
I don't know	0	0.0	0	0.0	0	0.0

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 10.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to<20 min**
- **S-3c - ≥20 min**

Demonstrated Understanding	S-3a <10 min N=50		S-3b 10 to <20 min N=81		S-3c ≥20 min N=20	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	1	2.0	1	1.2	0	0.0
2 correct responses	49	98.0	80	98.8	20	100.0
Average number of correct responses	2.0 (1.7, 2.0) [1]		2.0 (1.7, 2.0) [1]		2.0 (1.5, 2.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 11.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to<20 min**
- **S-3c - ≥20 min**

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=81		S-3c ≥20 min N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13a: TIRF medicines should be stored in a safe place out of the reach of children.						
True [1]	48	96.0 (86.3, 99.5)	81	100.0 (95.5, 100.0)	20	100.0 (83.2, 100.0)
False	1	2.0	0	0.0	0	0.0
I don't know	1	2.0	0	0.0	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.						
True [1]	46	92.0 (80.8, 97.8)	78	96.3 (89.6, 99.2)	19	95.0 (75.1, 99.9)
False	0	0.0	0	0.0	0	0.0
I don't know	4	8.0	3	3.7	1	5.0

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=81		S-3c ≥20 min N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
17e: A TIRF medicine can cause an overdose and death in any child who takes it.						
True [1]	46	92.0 (80.8, 97.8)	75	92.6 (84.6, 97.2)	17	85.0 (62.1, 96.8)
False	1	2.0	1	1.2	0	0.0
I don't know	3	6.0	5	6.2	3	15.0
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)						
Get emergency help right away. [1]	44	88.0 (75.7, 95.5)	74	91.4 (83.0, 96.5)	19	95.0 (75.1, 99.9)
Do nothing.	0	0.0	0	0.0	0	0.0
Wait an hour and see if the person is OK.	2	4.0	3	3.7	0	0.0
I don't know.	4	8.0	4	4.9	1	5.0

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 11.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to<20 min**
- **S-3c - ≥20 min**

Demonstrated Understanding	S-3a <10 min N=50		S-3b 10 to <20 min N=81		S-3c ≥20 min N=20	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	1	2.0	1	1.2	0	0.0
2 correct responses	1	2.0	3	3.7	1	5.0
3 correct responses	11	22.0	7	8.6	3	15.0
4 correct responses	37	74.0	70	86.4	16	80.0
Average number of correct responses	3.7 (3.2, 4.0) [1]		3.8 (3.4, 4.0) [1]		3.8 (3.0, 4.0) [1]	

[1] One-sided 95% confidence interval using the normal approximation to the Poisson distribution.

TABLE 6.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 1: TIRF MEDICINES CAN CAUSE LIFE-THREATENING BREATHING PROBLEMS THAT CAN LEAD TO DEATH.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to <20 min**
- **S-4c - ≥20 min**

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=47		S-4c ≥20 min N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.						
True [1]	0	-	41	87.2 (74.3, 95.2)	29	93.5 (78.6, 99.2)
False	0	-	0	0.0	1	3.2
I don't know	0	-	6	12.8	1	3.2

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to <20 min**
- **S-4c - ≥20 min**

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=47		S-4c ≥20 min N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statement:						
TIRF medicines should only be taken by patients who are opioid tolerant.						
True [1]	0	-	39	83.0 (69.2, 92.4)	22	71.0 (52.0, 85.8)
False	0	-	1	2.1	2	6.5
I don't know	0	-	7	14.9	7	22.6
Question 12: Please answer True, False, or I don't know for each of the following statements.						
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.						
True [1]	0	-	35	74.5 (59.7, 86.1)	25	80.6 (62.5, 92.5)
False	0	-	6	12.8	0	0.0
I don't know	0	-	6	12.8	6	19.4

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=47		S-4c ≥20 min N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13b: It is OK for patients to take TIRF medicines for headache pain.						
False [1]	0	-	32	68.1 (52.9, 80.9)	18	58.1 (39.1, 75.5)
True	0	-	2	4.3	4	12.9
I don't know	0	-	13	27.7	9	29.0

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to <20 min**
- **S-4c - ≥20 min**

Demonstrated Understanding	S-4a <10 min N=0		S-4b 10 to <20 min N=47		S-4c ≥20 min N=31	
	N	%	N	%	N	%
0 correct responses	0	-	3	6.4	2	6.5
1 correct response	0	-	5	10.6	3	9.7
2 correct responses	0	-	16	34.0	16	51.6
3 correct responses	0	-	23	48.9	10	32.3
Average number of correct responses	-		2.3 (1.9, 3.0) [1]		2.1 (1.7, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3 IN ELIGIBLE AND COMPLETE RESPONDENTS

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to <20 min**
- **S-4c - ≥20 min**

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=47		S-4c ≥20 min N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.						
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.						
True [1]	0	-	8	17.0 (7.6, 30.8)	10	32.3 (16.7, 51.4)
False	0	-	11	23.4	11	35.5
I don't know	0	-	28	59.6	10	32.3
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13c: TIRF medicines should be taken exactly as prescribed by the doctor.						
True [1]	0	-	47	100.0 (92.5, 100.0)	30	96.8 (83.3, 99.9)
False	0	-	0	0.0	1	3.2
I don't know	0	-	0	0.0	0	0.0

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=47		S-4c ≥20 min N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.						
False [1]	0	-	36	76.6 (62.0, 87.7)	25	80.6 (62.5, 92.5)
True	0	-	2	4.3	1	3.2
I don't know	0	-	9	19.1	5	16.1

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to <20 min**
- **S-4c - ≥20 min**

Demonstrated Understanding	S-4a <10 min N=0		S-4b 10 to <20 min N=47		S-4c ≥20 min N=31	
	N	%	N	%	N	%
0 correct responses	0	-	0	0.0	0	0.0
1 correct response	0	-	11	23.4	3	9.7
2 correct responses	0	-	28	59.6	22	71.0
3 correct responses	0	-	8	17.0	6	19.4
Average number of correct responses	-		1.9 (1.6, 3.0) [1]		2.1 (1.7, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 9.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4 IN ELIGIBLE AND COMPLETE RESPONDENTS

RISK MESSAGE 4: PATIENTS SHOULD NOT SWITCH FROM A TIRF MEDICINE TO ANOTHER MEDICINE THAT CONTAINS FENTANYL WITHOUT TALKING TO A HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to <20 min**
- **S-4c - ≥20 min**

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=47		S-4c ≥20 min N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.						
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.						
False [1]	0	-	47	100.0 (92.5, 100.0)	28	90.3 (74.2, 98.0)
True	0	-	0	0.0	0	0.0
I don't know	0	-	0	0.0	3	9.7

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 10.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to <20 min**
- **S-4c - ≥20 min**

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=47		S-4c ≥20 min N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.						
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.						
False [1]	0	-	46	97.9 (88.7, 99.9)	31	100.0 (88.8, 100.0)
True	0	-	0	0.0	0	0.0
I don't know	0	-	1	2.1	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17a: Selling or giving away TIRF medicines is against the law.						
True [1]	0	-	47	100.0 (92.5, 100.0)	30	96.8 (83.3, 99.9)
False	0	-	0	0.0	0	0.0
I don't know	0	-	0	0.0	1	3.2

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

Client: TRIG Project: TIRF Wave 3

Report Run Date and Time: 10/31/2014 2:21 PM

TABLE 10.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to <20 min**
- **S-4c - ≥20 min**

Demonstrated Understanding	S-4a <10 min N=0		S-4b 10 to <20 min N=47		S-4c ≥20 min N=31	
	N	%	N	%	N	%
0 correct responses	0	-	0	0.0	0	0.0
1 correct response	0	-	1	2.1	1	3.2
2 correct responses	0	-	46	97.9	30	96.8
Average number of correct responses	-		2.0 (1.6, 2.0) [1]		2.0 (1.6, 2.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 11.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to <20 min**
- **S-4c - ≥20 min**

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=47		S-4c ≥20 min N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13a: TIRF medicines should be stored in a safe place out of the reach of children.						
True [1]	0	-	47	100.0 (92.5, 100.0)	31	100.0 (88.8, 100.0)
False	0	-	0	0.0	0	0.0
I don't know	0	-	0	0.0	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.						
True [1]	0	-	42	89.4 (76.9, 96.5)	30	96.8 (83.3, 99.9)
False	0	-	0	0.0	0	0.0
I don't know	0	-	5	10.6	1	3.2

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=47		S-4c ≥20 min N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
17e: A TIRF medicine can cause an overdose and death in any child who takes it.						
True [1]	0	-	44	93.6 (82.5, 98.7)	25	80.6 (62.5, 92.5)
False	0	-	0	0.0	0	0.0
I don't know	0	-	3	6.4	6	19.4
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)						
Get emergency help right away. [1]	0	-	39	83.0 (69.2, 92.4)	26	83.9 (66.3, 94.5)
Do nothing.	0	-	0	0.0	0	0.0
Wait an hour and see if the person is OK.	0	-	1	2.1	1	3.2
I don't know.	0	-	7	14.9	4	12.9

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 11.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to <20 min**
- **S-4c - ≥20 min**

Demonstrated Understanding	S-4a <10 min N=0		S-4b 10 to <20 min N=47		S-4c ≥20 min N=31	
	N	%	N	%	N	%
0 correct responses	0	-	0	0.0	0	0.0
1 correct response	0	-	0	0.0	0	0.0
2 correct responses	0	-	2	4.3	2	6.5
3 correct responses	0	-	12	25.5	8	25.8
4 correct responses	0	-	33	70.2	21	67.7
Average number of correct responses	-		3.7 (3.2, 4.0) [1]		3.6 (3.1, 4.0) [1]	

[1] One-sided 95% confidence interval using the normal approximation to the Poisson distribution.

TABLE 6.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 1: TIRF MEDICINES CAN CAUSE LIFE-THREATENING BREATHING PROBLEMS THAT CAN LEAD TO DEATH.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Question	S-5a Internet N=151		S-5b Telephone N=78	
	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.				
True [1]	139	92.1 (86.5, 95.8)	70	89.7 (80.8, 95.5)
False	0	0.0	1	1.3
I don't know	12	7.9	7	9.0

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Question	S-5a Internet N=151		S-5b Telephone N=78	
	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statement:				
TIRF medicines should only be taken by patients who are opioid tolerant.				
True [1]	134	88.7 (82.6, 93.3)	61	78.2 (67.4, 86.8)
False	3	2.0	3	3.8
I don't know	14	9.3	14	17.9
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.				
True [1]	127	84.1 (77.3, 89.5)	60	76.9 (66.0, 85.7)
False	13	8.6	6	7.7
I don't know	11	7.3	12	15.4

Question	S-5a Internet N=151		S-5b Telephone N=78	
	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13b: It is OK for patients to take TIRF medicines for headache pain.				
False [1]	109	72.2 (64.3, 79.2)	50	64.1 (52.4, 74.7)
True	10	6.6	6	7.7
I don't know	32	21.2	22	28.2

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Demonstrated Understanding	S-5a Internet N=151		S-5b Telephone N=78	
	N	%	N	%
0 correct responses	5	3.3	5	6.4
1 correct response	13	8.6	8	10.3
2 correct responses	42	27.8	32	41.0
3 correct responses	91	60.3	33	42.3
Average number of correct responses	2.5 (2.2, 3.0) [1]		2.2 (1.9, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3 IN ELIGIBLE AND COMPLETE RESPONDENTS

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Question	S-5a Internet N=151		S-5b Telephone N=78	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.				
True [1]	66	43.7 (35.7, 52.0)	18	23.1 (14.3, 34.0)
False	36	23.8	22	28.2
I don't know	49	32.5	38	48.7
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13c: TIRF medicines should be taken exactly as prescribed by the doctor.				
True [1]	150	99.3 (96.4, 100.0)	77	98.7 (93.1, 100.0)
False	1	0.7	1	1.3
I don't know	0	0.0	0	0.0

Question	S-5a Internet N=151		S-5b Telephone N=78	
	N	% (95% CI)	N	% (95% CI)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.				
False [1]	129	85.4 (78.8, 90.6)	61	78.2 (67.4, 86.8)
True	9	6.0	3	3.8
I don't know	13	8.6	14	17.9

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Demonstrated Understanding	S-5a Internet N=151		S-5b Telephone N=78	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	16	10.6	14	17.9
2 correct responses	76	50.3	50	64.1
3 correct responses	59	39.1	14	17.9
Average number of correct responses	2.3 (2.1, 3.0) [1]		2.0 (1.7, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 9.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4 IN ELIGIBLE AND COMPLETE RESPONDENTS

RISK MESSAGE 4: PATIENTS SHOULD NOT SWITCH FROM A TIRF MEDICINE TO ANOTHER MEDICINE THAT CONTAINS FENTANYL WITHOUT TALKING TO A HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Question	S-5a Internet N=151		S-5b Telephone N=78	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.				
False [1]	147	97.4 (93.4, 99.3)	75	96.2 (89.2, 99.2)
True	2	1.3	0	0.0
I don't know	2	1.3	3	3.8

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 10.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Question	S-5a Internet N=151		S-5b Telephone N=78	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.				
False [1]	150	99.3 (96.4, 100.0)	77	98.7 (93.1, 100.0)
True	1	0.7	0	0.0
I don't know	0	0.0	1	1.3
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17a: Selling or giving away TIRF medicines is against the law.				
True [1]	150	99.3 (96.4, 100.0)	77	98.7 (93.1, 100.0)
False	1	0.7	0	0.0
I don't know	0	0.0	1	1.3

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 10.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Demonstrated Understanding	S-5a Internet N=151		S-5b Telephone N=78	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	2	1.3	2	2.6
2 correct responses	149	98.7	76	97.4
Average number of correct responses	2.0 (1.8, 2.0) [1]		2.0 (1.7, 2.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 11.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Question	S-5a Internet N=151		S-5b Telephone N=78	
	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13a: TIRF medicines should be stored in a safe place out of the reach of children.				
True [1]	149	98.7 (95.3, 99.8)	78	100.0 (95.4, 100.0)
False	1	0.7	0	0.0
I don't know	1	0.7	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.				
True [1]	143	94.7 (89.8, 97.7)	72	92.3 (84.0, 97.1)
False	0	0.0	0	0.0
I don't know	8	5.3	6	7.7
17e: A TIRF medicine can cause an overdose and death in any child who takes it.				
True [1]	138	91.4 (85.7, 95.3)	69	88.5 (79.2, 94.6)
False	2	1.3	0	0.0
I don't know	11	7.3	9	11.5

Question	S-5a Internet N=151		S-5b Telephone N=78	
	N	% (95% CI)	N	% (95% CI)
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)				
Get emergency help right away. [1]	137	90.7 (84.9, 94.8)	65	83.3 (73.2, 90.8)
Do nothing.	0	0.0	0	0.0
Wait an hour and see if the person is OK.	5	3.3	2	2.6
I don't know.	9	6.0	11	14.1

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 11.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Demonstrated Understanding	S-5a Internet N=151		S-5b Telephone N=78	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	2	1.3	0	0.0
2 correct responses	5	3.3	4	5.1
3 correct responses	21	13.9	20	25.6
4 correct responses	123	81.5	54	69.2
Average number of correct responses	3.8 (3.5, 4.0) [1]		3.6 (3.3, 4.0) [1]	

[1] One-sided 95% confidence interval using the normal approximation to the Poisson distribution.

TABLE 6.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 1: TIRF MEDICINES CAN CAUSE LIFE-THREATENING BREATHING PROBLEMS THAT CAN LEAD TO DEATH.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a – Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate's degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Question	S-6a High School N=42		S-6b Some college N=102		S-6c Bachelor or Master N=71		S-6d Doctoral degree N=14	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.								
True [1]	36	85.7 (71.5, 94.6)	92	90.2 (82.7, 95.2)	69	97.2 (90.2, 99.7)	12	85.7 (57.2, 98.2)
False	0	0.0	1	1.0	0	0.0	0	0.0
I don't know	6	14.3	9	8.8	2	2.8	2	14.3

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a – Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate's degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Question	S-6a High School N=42		S-6b Some college N=102		S-6c Bachelor or Master N=71		S-6d Doctoral degree N=14	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statement:								
TIRF medicines should only be taken by patients who are opioid tolerant.								
True [1]	29	69.0 (52.9, 82.4)	90	88.2 (80.4, 93.8)	64	90.1 (80.7, 95.9)	12	85.7 (57.2, 98.2)
False	3	7.1	2	2.0	1	1.4	0	0.0
I don't know	10	23.8	10	9.8	6	8.5	2	14.3

Question	S-6a High School N=42		S-6b Some college N=102		S-6c Bachelor or Master N=71		S-6d Doctoral degree N=14	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.								
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.								
True [1]	32	76.2 (60.5, 87.9)	86	84.3 (75.8, 90.8)	60	84.5 (74.0, 92.0)	9	64.3 (35.1, 87.2)
False	5	11.9	9	8.8	4	5.6	1	7.1
I don't know	5	11.9	7	6.9	7	9.9	4	28.6
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13b: It is OK for patients to take TIRF medicines for headache pain.								
False [1]	24	57.1 (41.0, 72.3)	69	67.6 (57.7, 76.6)	55	77.5 (66.0, 86.5)	11	78.6 (49.2, 95.3)
True	3	7.1	8	7.8	4	5.6	1	7.1
I don't know	15	35.7	25	24.5	12	16.9	2	14.3

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a – Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate's degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Demonstrated Understanding	S-6a High School N=42		S-6b Some college N=102		S-6c Bachelor or Master N=71		S-6d Doctoral degree N=14	
	N	%	N	%	N	%	N	%
0 correct responses	3	7.1	4	3.9	2	2.8	1	7.1
1 correct response	7	16.7	8	7.8	4	5.6	2	14.3
2 correct responses	18	42.9	33	32.4	20	28.2	3	21.4
3 correct responses	14	33.3	57	55.9	45	63.4	8	57.1
Average number of correct responses	2.0 (1.7, 3.0) [1]		2.4 (2.1, 3.0) [1]		2.5 (2.2, 3.0) [1]		2.3 (1.6, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3 IN ELIGIBLE AND COMPLETE RESPONDENTS

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a – Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate's degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Question	S-6a High School N=42		S-6b Some college N=102		S-6c Bachelor or Master N=71		S-6d Doctoral degree N=14	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.								
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.								
True [1]	8	19.0 (8.6, 34.1)	41	40.2 (30.6, 50.4)	30	42.3 (30.6, 54.6)	5	35.7 (12.8, 64.9)
False	12	28.6	21	20.6	21	29.6	4	28.6
I don't know	22	52.4	40	39.2	20	28.2	5	35.7

Question	S-6a High School N=42		S-6b Some college N=102		S-6c Bachelor or Master N=71		S-6d Doctoral degree N=14	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13c: TIRF medicines should be taken exactly as prescribed by the doctor.								
True [1]	42	100.0 (91.6, 100.0)	101	99.0 (94.7, 100.0)	70	98.6 (92.4, 100.0)	14	100.0 (76.8, 100.0)
False	0	0.0	1	1.0	1	1.4	0	0.0
I don't know	0	0.0	0	0.0	0	0.0	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.								
False [1]	35	83.3 (68.6, 93.0)	80	78.4 (69.2, 86.0)	63	88.7 (79.0, 95.0)	12	85.7 (57.2, 98.2)
True	1	2.4	10	9.8	1	1.4	0	0.0
I don't know	6	14.3	12	11.8	7	9.9	2	14.3

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a – Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate's degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Demonstrated Understanding	S-6a High School N=42		S-6b Some college N=102		S-6c Bachelor or Master N=71		S-6d Doctoral degree N=14	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	6	14.3	15	14.7	7	9.9	2	14.3
2 correct responses	29	69.0	54	52.9	36	50.7	7	50.0
3 correct responses	7	16.7	33	32.4	28	39.4	5	35.7
Average number of correct responses	2.0 (1.7, 3.0) [1]		2.2 (1.9, 3.0) [1]		2.3 (2.0, 3.0) [1]		2.2 (1.6, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 9.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4 IN ELIGIBLE AND COMPLETE RESPONDENTS

RISK MESSAGE 4: PATIENTS SHOULD NOT SWITCH FROM A TIRF MEDICINE TO ANOTHER MEDICINE THAT CONTAINS FENTANYL WITHOUT TALKING TO A HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a – Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate's degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Question	S-6a High School N=42		S-6b Some college N=102		S-6c Bachelor or Master N=71		S-6d Doctoral degree N=14	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.								
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.								
False [1]	41	97.6 (87.4, 99.9)	99	97.1 (91.6, 99.4)	69	97.2 (90.2, 99.7)	13	92.9 (66.1, 99.8)
True	0	0.0	1	1.0	1	1.4	0	0.0
I don't know	1	2.4	2	2.0	1	1.4	1	7.1

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 10.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a – Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate's degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Question	S-6a High School N=42		S-6b Some college N=102		S-6c Bachelor or Master N=71		S-6d Doctoral degree N=14	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.								
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.								
False [1]	42	100.0 (91.6, 100.0)	101	99.0 (94.7, 100.0)	70	98.6 (92.4, 100.0)	14	100.0 (76.8, 100.0)
True	0	0.0	1	1.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	1	1.4	0	0.0

Question	S-6a High School N=42		S-6b Some college N=102		S-6c Bachelor or Master N=71		S-6d Doctoral degree N=14	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17a: Selling or giving away TIRF medicines is against the law.								
True [1]	42	100.0 (91.6, 100.0)	101	99.0 (94.7, 100.0)	70	98.6 (92.4, 100.0)	14	100.0 (76.8, 100.0)
False	0	0.0	0	0.0	1	1.4	0	0.0
I don't know	0	0.0	1	1.0	0	0.0	0	0.0

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 10.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a – Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate's degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Demonstrated Understanding	S-6a High School N=42		S-6b Some college N=102		S-6c Bachelor or Master N=71		S-6d Doctoral degree N=14	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	2	2.0	2	2.8	0	0.0
2 correct responses	42	100.0	100	98.0	69	97.2	14	100.0
Average number of correct responses	2.0 (1.6, 2.0) [1]		2.0 (1.8, 2.0) [1]		2.0 (1.7, 2.0) [1]		2.0 (1.4, 2.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 11.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a – Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate's degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Question	S-6a High School N=42		S-6b Some college N=102		S-6c Bachelor or Master N=71		S-6d Doctoral degree N=14	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13a: TIRF medicines should be stored in a safe place out of the reach of children.								
True [1]	41	97.6 (87.4, 99.9)	101	99.0 (94.7, 100.0)	71	100.0 (94.9, 100.0)	14	100.0 (76.8, 100.0)
False	0	0.0	1	1.0	0	0.0	0	0.0
I don't know	1	2.4	0	0.0	0	0.0	0	0.0

Question	S-6a High School N=42		S-6b Some college N=102		S-6c Bachelor or Master N=71		S-6d Doctoral degree N=14	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.								
True [1]	38	90.5 (77.4, 97.3)	96	94.1 (87.6, 97.8)	68	95.8 (88.1, 99.1)	13	92.9 (66.1, 99.8)
False	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	4	9.5	6	5.9	3	4.2	1	7.1
17e: A TIRF medicine can cause an overdose and death in any child who takes it.								
True [1]	36	85.7 (71.5, 94.6)	93	91.2 (83.9, 95.9)	65	91.5 (82.5, 96.8)	13	92.9 (66.1, 99.8)
False	0	0.0	0	0.0	2	2.8	0	0.0
I don't know	6	14.3	9	8.8	4	5.6	1	7.1

Question	S-6a High School N=42		S-6b Some college N=102		S-6c Bachelor or Master N=71		S-6d Doctoral degree N=14	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)								
Get emergency help right away. [1]	38	90.5 (77.4, 97.3)	91	89.2 (81.5, 94.5)	63	88.7 (79.0, 95.0)	10	71.4 (41.9, 91.6)
Do nothing.	0	0.0	0	0.0	0	0.0	0	0.0
Wait an hour and see if the person is OK.	3	7.1	1	1.0	3	4.2	0	0.0
I don't know.	1	2.4	10	9.8	5	7.0	4	28.6

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 11.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a – Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate's degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Demonstrated Understanding	S-6a High School N=42		S-6b Some college N=102		S-6c Bachelor or Master N=71		S-6d Doctoral degree N=14	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	1	2.4	1	1.0	0	0.0	0	0.0
2 correct responses	0	0.0	4	3.9	3	4.2	2	14.3
3 correct responses	12	28.6	16	15.7	11	15.5	2	14.3
4 correct responses	29	69.0	81	79.4	57	80.3	10	71.4
Average number of correct responses	3.6 (3.2, 4.0) [1]		3.7 (3.4, 4.0) [1]		3.8 (3.4, 4.0) [1]		3.6 (2.7, 4.0) [1]	

[1] One-sided 95% confidence interval using the normal approximation to the Poisson distribution.

TABLE 6.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 1: TIRF MEDICINES CAN CAUSE LIFE-THREATENING BREATHING PROBLEMS THAT CAN LEAD TO DEATH.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Question	S-7a 18 to 39 N=30		S-7b 40 to 49 N=65		S-7c 50 to 59 N=88		S-7d 60 or older N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.								
True [1]	26	86.7 (69.3, 96.2)	62	95.4 (87.1, 99.0)	79	89.8 (81.5, 95.2)	42	91.3 (79.2, 97.6)
False	0	0.0	0	0.0	0	0.0	1	2.2
I don't know	4	13.3	3	4.6	9	10.2	3	6.5

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Question	S-7a 18 to 39 N=30		S-7b 40 to 49 N=65		S-7c 50 to 59 N=88		S-7d 60 or older N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statement:								
TIRF medicines should only be taken by patients who are opioid tolerant.								
True [1]	26	86.7 (69.3, 96.2)	57	87.7 (77.2, 94.5)	75	85.2 (76.1, 91.9)	37	80.4 (66.1, 90.6)
False	0	0.0	3	4.6	2	2.3	1	2.2
I don't know	4	13.3	5	7.7	11	12.5	8	17.4

Question	S-7a 18 to 39 N=30		S-7b 40 to 49 N=65		S-7c 50 to 59 N=88		S-7d 60 or older N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.								
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.								
True [1]	24	80.0 (61.4, 92.3)	58	89.2 (79.1, 95.6)	70	79.5 (69.6, 87.4)	35	76.1 (61.2, 87.4)
False	1	3.3	4	6.2	8	9.1	6	13.0
I don't know	5	16.7	3	4.6	10	11.4	5	10.9
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13b: It is OK for patients to take TIRF medicines for headache pain.								
False [1]	20	66.7 (47.2, 82.7)	46	70.8 (58.2, 81.4)	61	69.3 (58.6, 78.7)	32	69.6 (54.2, 82.3)
True	3	10.0	4	6.2	7	8.0	2	4.3
I don't know	7	23.3	15	23.1	20	22.7	12	26.1

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Demonstrated Understanding	S-7a 18 to 39 N=30		S-7b 40 to 49 N=65		S-7c 50 to 59 N=88		S-7d 60 or older N=46	
	N	%	N	%	N	%	N	%
0 correct responses	2	6.7	1	1.5	5	5.7	2	4.3
1 correct response	3	10.0	5	7.7	7	8.0	6	13.0
2 correct responses	8	26.7	21	32.3	29	33.0	16	34.8
3 correct responses	17	56.7	38	58.5	47	53.4	22	47.8
Average number of correct responses	2.3 (1.9, 3.0) [1]		2.5 (2.2, 3.0) [1]		2.3 (2.1, 3.0) [1]		2.3 (1.9, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3 IN ELIGIBLE AND COMPLETE RESPONDENTS

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Question	S-7a 18 to 39 N=30		S-7b 40 to 49 N=65		S-7c 50 to 59 N=88		S-7d 60 or older N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.								
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.								
True [1]	10	33.3 (17.3, 52.8)	25	38.5 (26.7, 51.4)	32	36.4 (26.4, 47.3)	17	37.0 (23.2, 52.5)
False	6	20.0	15	23.1	21	23.9	16	34.8
I don't know	14	46.7	25	38.5	35	39.8	13	28.3

Question	S-7a 18 to 39 N=30		S-7b 40 to 49 N=65		S-7c 50 to 59 N=88		S-7d 60 or older N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13c: TIRF medicines should be taken exactly as prescribed by the doctor.								
True [1]	30	100.0 (88.4, 100.0)	64	98.5 (91.7, 100.0)	87	98.9 (93.8, 100.0)	46	100.0 (92.3, 100.0)
False	0	0.0	1	1.5	1	1.1	0	0.0
I don't know	0	0.0	0	0.0	0	0.0	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.								
False [1]	21	70.0 (50.6, 85.3)	58	89.2 (79.1, 95.6)	72	81.8 (72.2, 89.2)	39	84.8 (71.1, 93.7)
True	1	3.3	2	3.1	8	9.1	1	2.2
I don't know	8	26.7	5	7.7	8	9.1	6	13.0

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Demonstrated Understanding	S-7a 18 to 39 N=30		S-7b 40 to 49 N=65		S-7c 50 to 59 N=88		S-7d 60 or older N=46	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	8	26.7	7	10.8	10	11.4	5	10.9
2 correct responses	13	43.3	34	52.3	53	60.2	26	56.5
3 correct responses	9	30.0	24	36.9	25	28.4	15	32.6
Average number of correct responses	2.0 (1.6, 3.0) [1]		2.3 (2.0, 3.0) [1]		2.2 (1.9, 3.0) [1]		2.2 (1.9, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 9.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4 IN ELIGIBLE AND COMPLETE RESPONDENTS

RISK MESSAGE 4: PATIENTS SHOULD NOT SWITCH FROM A TIRF MEDICINE TO ANOTHER MEDICINE THAT CONTAINS FENTANYL WITHOUT TALKING TO A HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Question	S-7a 18 to 39 N=30		S-7b 40 to 49 N=65		S-7c 50 to 59 N=88		S-7d 60 or older N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.								
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.								
False [1]	30	100.0 (88.4, 100.0)	64	98.5 (91.7, 100.0)	85	96.6 (90.4, 99.3)	43	93.5 (82.1, 98.6)
True	0	0.0	1	1.5	0	0.0	1	2.2
I don't know	0	0.0	0	0.0	3	3.4	2	4.3

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 10.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Question	S-7a 18 to 39 N=30		S-7b 40 to 49 N=65		S-7c 50 to 59 N=88		S-7d 60 or older N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.								
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.								
False [1]	30	100.0 (88.4, 100.0)	64	98.5 (91.7, 100.0)	88	100.0 (95.9, 100.0)	45	97.8 (88.5, 99.9)
True	0	0.0	1	1.5	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0	1	2.2

Question	S-7a 18 to 39 N=30		S-7b 40 to 49 N=65		S-7c 50 to 59 N=88		S-7d 60 or older N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17a: Selling or giving away TIRF medicines is against the law.								
True [1]	30	100.0 (88.4, 100.0)	64	98.5 (91.7, 100.0)	87	98.9 (93.8, 100.0)	46	100.0 (92.3, 100.0)
False	0	0.0	1	1.5	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	1	1.1	0	0.0

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 10.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Demonstrated Understanding	S-7a 18 to 39 N=30		S-7b 40 to 49 N=65		S-7c 50 to 59 N=88		S-7d 60 or older N=46	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	2	3.1	1	1.1	1	2.2
2 correct responses	30	100.0	63	96.9	87	98.9	45	97.8
Average number of correct responses	2.0 (1.6, 2.0) [1]		2.0 (1.7, 2.0) [1]		2.0 (1.7, 2.0) [1]		2.0 (1.6, 2.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 11.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Question	S-7a 18 to 39 N=30		S-7b 40 to 49 N=65		S-7c 50 to 59 N=88		S-7d 60 or older N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13a: TIRF medicines should be stored in a safe place out of the reach of children.								
True [1]	30	100.0 (88.4, 100.0)	64	98.5 (91.7, 100.0)	87	98.9 (93.8, 100.0)	46	100.0 (92.3, 100.0)
False	0	0.0	0	0.0	1	1.1	0	0.0
I don't know	0	0.0	1	1.5	0	0.0	0	0.0

Question	S-7a 18 to 39 N=30		S-7b 40 to 49 N=65		S-7c 50 to 59 N=88		S-7d 60 or older N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.								
True [1]	29	96.7 (82.8, 99.9)	58	89.2 (79.1, 95.6)	84	95.5 (88.8, 98.7)	44	95.7 (85.2, 99.5)
False	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	1	3.3	7	10.8	4	4.5	2	4.3
17e: A TIRF medicine can cause an overdose and death in any child who takes it.								
True [1]	28	93.3 (77.9, 99.2)	62	95.4 (87.1, 99.0)	77	87.5 (78.7, 93.6)	40	87.0 (73.7, 95.1)
False	0	0.0	0	0.0	2	2.3	0	0.0
I don't know	2	6.7	3	4.6	9	10.2	6	13.0

Question	S-7a 18 to 39 N=30		S-7b 40 to 49 N=65		S-7c 50 to 59 N=88		S-7d 60 or older N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)								
Get emergency help right away. [1]	27	90.0 (73.5, 97.9)	57	87.7 (77.2, 94.5)	79	89.8 (81.5, 95.2)	39	84.8 (71.1, 93.7)
Do nothing.	0	0.0	0	0.0	0	0.0	0	0.0
Wait an hour and see if the person is OK.	1	3.3	3	4.6	1	1.1	2	4.3
I don't know.	2	6.7	5	7.7	8	9.1	5	10.9

[1] Correct response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 11.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6 IN ELIGIBLE AND COMPLETE RESPONDENTS

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Demonstrated Understanding	S-7a 18 to 39 N=30		S-7b 40 to 49 N=65		S-7c 50 to 59 N=88		S-7d 60 or older N=46	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	1	3.3	1	1.5	0	0.0	0	0.0
2 correct responses	0	0.0	1	1.5	3	3.4	5	10.9
3 correct responses	3	10.0	14	21.5	19	21.6	5	10.9
4 correct responses	26	86.7	49	75.4	66	75.0	36	78.3
Average number of correct responses	3.8 (3.2, 4.0) [1]		3.7 (3.3, 4.0) [1]		3.7 (3.4, 4.0) [1]		3.7 (3.2, 4.0) [1]	

[1] One-sided 95% confidence interval using the normal approximation to the Poisson distribution.

Listing 1 **VERBATIM RESPONSES TO QUESTION 22 (How frequently do you receive a Medication Guide for the TIRF medicine at the pharmacy?)**

Verbatim Response
every other time
(b) (4) pharmacy
Every couple months
with every new box
only had gotten once
There is a Medication Guide in each box of Fentora I receive

Listing 2 **VERBATIM RESPONSES TO QUESTION 27 (Other person offering explanation of the Medication Guide)**

Verbatim Response
Drug Representative for the study
Epocrates PDA app for handling medication interactions
home nurse
Nurse
Pharmacy Tech
Pharmacy Tech filling my script
spouse
The PA
(b) (4) Pharmacy Technician

Listing 3 VERBATIM RESPONSES TO QUESTION 30 (Questions about the information in the Medication Guide)

Verbatim Response
about the kit I should get & also got questions answered in past as I called 1-800 # & asked to help understand them but can't remember now as I have been on this medication for like 13+ yrs
Don't remember..
Effects of long term use and recognizing withdrawal symptoms
How do I find if my pharmacy is registered? They directed me to the web page and the phone number to call for any questions.
How taking the medication affects your bladder?
I mentioned to the doc once that I swallowed the drug (according to the instruction in the guide), and he said I should never do that b/c then I wouldn't get any benefit from the swallowed drug, so my questions are (1)how can I accelerate the dissolution of the drug and (2)why does the guide say to swallow it if (presumably) stomach acids wipe it out?
i was told it is ok to take long term?
I would have appreciated it if at the outset someone had explained to me how difficult it is to stop taking opiod therapy before I made the decision to go onto such therapy.
It was more than four years ago; I do not remember. (b) (4) Pharmacist answered the 1 or 2 questions I had.
Proper disposal of unfinished medication
The important information was not in the literature
The question (which has been answered) was related to the dosage.
When you put the transdermal patch on how long does it take before it starts to work? 24 hours or immediately?
Where can I get the container for the empty lollipops?
WHY SO EXPENSIVE?

Listing 4 **REPORTED ADVERSE EVENTS, PRODUCT COMPLAINTS, or Requests for Medical Information**

Verbatim Response
"Been having troubles with my bladder since I started taking it."
"hard time moving around"
"I get depressed and I can't sleep at night", "I have pain management for my pain", "just came home from hospital, for steroid shots, due to tears in my arms", "I'm not well", "I'm in severe pain, it's a little difficult today", "I have a lump they found in my breast", " and in my stomach, I'm waiting for that to come back", "because they found lumps all in my body all over me", "it started when I called just had sharp pain in my arm, it's killing me"
"I have headaches". "I had an allergic reaction to Subsys". "I had breathing problems and seizures with that reaction before". "I have cluster migraines". "I have had a neck injury".
"I wish they would have included the important stuff in the literature about dry mouth and messing with your enamel, I found out from my Dentist"

Verbatim Response
"nausea", 50lb weight loss with in 3 weeks. Not eaten in 3 days with vomiting and diarrhea last week. Chronic Pancreatitis. Took a shot for diarrhea and it made sick. 25AUG2014 @ 4:59 PM "You know something, I had a lot of trouble this month Merck/Medco was the cause of it. Even though my doctor made a human error – merck did get the proper information in time enough to send them out. In [redacted] (b) (6) we are only allowed a 30 day supply. I had to wear 1 patch instead of 2 for like 10 days. Not a single pharmacist explained it to me all they kept saying was do you want brand or generic. I told them just as the doctor has written it. They finally got it straight and I never received it until, until like the 12th." "I was sick for 2 weeks; I haven't eaten in 3 days. I've lost 50 pounds in 3 weeks because I haven't been able to eat and I don't know if it's because of the patches but they must work. I did not overuse the lozenges I only use what the doctor tells me" "Par pharmaceutical sends me the overlays for the patches because they don't stay on my skin" "I still get close to running out but it wasn't actually until this last month that I did run out and I had to decrease to 1 instead of 2" "Yes what's happened is I've lost so much weight, all my teeth fell out after radiation" "This past month I asked the pharmacist at Merck/Medco what should I do that I was out of medicine, and I had to go down to 1 patch and if that was ok or not ok, and they never answered" "It was his human error, he forgot to put the micrograms on there, it was remedied immediately but they didn't fill it correctly" "It wouldn't stay on my skin; I used duct tape for a while til I finally got Par Pharmaceuticals to send me an overlay" "I have severe diarrhea and throwing up last month it was both at the same time" "My diarrhea comes in spurts of maybe several times a month then it clears up and I'm ok" "I could take a shot for the diarrhea but it made me really ill the last time"
"That's why I take it" (Long-lasting painful conditions not caused by cancer) Question 11
"True – you have to have heavy duty migraine pain like I have" "I have got nerve damage that leads to migraine type pain" "I've got a bad memory – the doctor says it isn't Alzheimer's but I believe it is."

Verbatim Response
"Where can I get the container for the empty lollipops? If I do the whole thing at once I pass out. It's just to much medicine and it makes me fall asleep not pass out. It makes me drowsy and fall asleep. I have a lot of health problems."
"you mean pain from my shingles" this was in reference to him answering page 11
"No, I'm not using it for that even though I was told it could be used it for that" Q10 (Breakthrough pain from cancer)
"technically it's no, but I've been using it for migraines. Because none of the other medicines work, and I have a rare migraine disease." "For me, yes, but technically, no." "Because when I have a migraine, I end up having strokes."
Chronic Back injuries Q10 I have chronic back and cancer
I asked the Dr about the side effects and he didn't know about them. He doesn't know what my side effects should be. I've been on pain meds for a long time and what he is telling me it is supposed to be doing, it isn't doing. It isn't lasting long. "I have true pain."
I get tired all the time. I have a problem getting this medication because Medicare says hysil psycosis isn't cancer even though I am on Chemo for it and it's very painful and nothing else works for me. I have psoriatic arthritis and hysil psychosis, which hysil psychosis is very rare and there isn't a lot of studies on it but it's just like cancer.
I have a cold
I have tumor pain in my head
I'm not feeling well. I'm on chemo and some days I have good days others not so.
I'm sick; I'm terminally ill. I have PSD and Fibromyalgia; I had my knees replaced - it's eating away at my legs and bladder, it's like cancer- I have seizures to.
I've been in the hospital so long" "Prescribed for back pain"
Keeps falling off the sticks. Breaks apart off the stick they don't work properly and the cost is ridiculous when they don't work. She said it only works 45 minutes and then the pain is back.
This product is so expensive if I didn't have health insurance I could never afford it. I have never seen a prescription be so costly.
about the kit I should get & also got questions answered in past as I called 1-800 # & asked to help understand them but can't remember now as I have been on this medication for like 13+ yrs
Effects of long term use and recognizing withdrawal symptoms

Verbatim Response
How taking the medication affects your bladder?
I mentioned to the doc once that I swallowed the drug (according to the instruction in the guide), and he said I should never do that b/c then I wouldn't get any benefit from the swallowed drug, so my questions are (1)how can I accelerate the dissolution of the drug and (2)why does the guide say to swallow it if (presumably) stomach acids wipe it out?
i was told it is ok to take long term?
I would have appreciated it if at the outset someone had explained to me how difficult it is to stop taking opiod therapy before I made the decision to go onto such therapy.
Proper disposal of unfinished medication
The important information was not in the literature
When you put the transdermal patch on how long does it take before it starts to work? 24 hours or immediately?
Where can I get the container for the empty lollipops?
WHY SO EXPENSIVE?
I have a heart monitor and I have severe cramping in my left leg it's only happened a couple of times I think I am going to go see me heart Dr. just to be safe
"History of migraines, and its not the migraines its problems with my neck that causes pain in my head."
"Just changed the medicine because I didn't like it. Their to sweet, they had the original one that tasted like chalk and then they switched to the new ones that taste like sugar. New medication doesn't seem to work like old medicine. It dissolves to fast to much sugar. think it dissolves to fast because it dissolves in 5 minutes. Doesn't last but 5 minutes."
I can't swallow, so these medications are a god send to me. I wanted to make you aware that I recently changed from Actiq back to Fentora because the Actiq was messing up my teeth. I had oral cancer and issues with my mouth. The Actiq was causing pain in my mouth". "It caused a lot of accelerated damage to my teeth so I had to stop taking it". "Where I had to place it, it burns and was hurting my mouth". "It got to the point where I could barely even keep them in my mouth because of the pain"

Appendix C Patient Survey Protocol Track Change Document: Comparison of 24-month Survey to 36-month Survey

PROTOCOL TITLE:	**Quantitative Testing of Patient/Caregiver Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)**
	Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)
	Depomed, Inc.
	Galena Biopharma, Inc.
	Insys Therapeutics
	Mallinckrodt Pharmaceuticals
	Meda Pharmaceuticals
	Mylan, Inc.
	Par Pharmaceutical, Inc.
VERSION:	**7.0**
DATE:	**18MAY2014**
APPROVED:	**Final**

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TABLE OF CONTENTS PAGE

	TABLE OF CONTENTS	2
1.	LIST OF ABBREVIATIONS	3
2.	BACKGROUND	4
3.	OBJECTIVES OF THE EVALUATION SURVEY	5
4.	METHODS	5
4.1	Qualitative Research on the Survey	5
4.2	Survey Design	5
4.2.1	Questions and Statements on REMS Goals	6
4.2.2	Additional Questions	9
4.3	Subject Recruitment	9
4.3.1	Measures to Minimize Bias in the Sample	10
5.	STUDY POPULATION	11
5.1.1	Sample Size	11
5.1.2	Inclusion Criteria	11
5.1.3	Exclusion Criteria	12
6.	SURVEY PROCESS	12
6.1	Screening and Survey Administration	12
6.1.1	Telephone	12
6.1.2	Internet	12
6.2	Measures to Minimize Bias in the Survey Process	13
7.	ANALYSIS	13
8.	SAFETY EVENT REPORTING	14
9.	PRIVACY PROTECTION AND CONFIDENTIALITY	14

LIST OF APPENDICES

APPENDIX A	Screening and Main Questionnaire	16
APPENDIX B	SAMPLE Patient Letter of Invitation	41

1. LIST OF ABBREVIATIONS

CATI	Computer-Assisted Telephone Interviewing
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
KAB	Knowledge, Attitudes and Behavior
PBM	Pharmacy Benefits Management
PPAF	Patient-Prescriber Agreement Form
REMS	Risk Evaluation and Mitigation Strategy
SE PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access Program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

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2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics, which are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risks of misuse, abuse, addiction, overdose and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients
2. Preventing inappropriate conversion between TIRF medicines
3. Preventing accidental exposure to children and others for whom it was not prescribed
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess patients' and caregivers' knowledge, attitudes, and behavior (KAB) regarding the safe use of TIRF medicines as described in the product-specific Medication Guide. This protocol will describe the administration of the surveys that will be conducted among patients who are treated with TIRF medicines, or their caregivers. Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes and/or educational materials to make them more effective in achieving the goals of the REMS.

The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

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3. OBJECTIVES OF THE EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of patients around the following key information and risk messages communicated through the REMS:

1) TIRF medicines can cause life-threatening breathing problems that can lead to death.
2) Patients should not take TIRF medicines if they are not opioid tolerant.
3) TIRF medicines should be taken exactly as prescribed by the healthcare provider.
4) Patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.
5) Patients should not give TIRF medicines to anyone else even if they have the same symptoms.
6) TIRF medicines should be stored in a safe place away from children and properly disposed.

The survey will also include questions about whether patients received, read, and understood the product-specific Medication Guide and Patient-Prescriber Agreement Form (PPAF).

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC), and will be administered by UBC.

4.1 Qualitative Research on the Survey

Qualitative research to test patient comprehension was performed on the patient survey in 2012. Findings were incorporated into the survey prior to implementation of Wave 1.

4.2 Survey Design

This survey will be conducted among a sample of patients or their caregivers who have filled a prescription for a TIRF medicine within the past 4 months prior to survey launch. Respondents who have participated in a previous wave of the TIRF REMS KAB survey will not be eligible to participate in subsequent survey waves.

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The survey will be administered using the following modalities:

- Self-administered, online through a secure website

- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

The survey included in Appendix B is written to reflect wording for both methods of survey administration: Internet-based and telephone administration.

4.2.1 Questions and Statements on REMS Goals

The questionnaire is made up of multiple-choice, closed-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and open-ended questions. These will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3. The survey is written to follow principles of health literacy and readability.

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Questionnaire items will be presented in several formats:

- Statements or questions asking the respondent to indicate whether the statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use "yes," "no," or "I don't know" as potential response options);

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- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and

- Questions allowing for the respondent to provide information about when, where and from whom they obtained a Medication Guide, as well as to list questions they have about information in the Medication Guides.

Questionnaires will be analyzed to determine patient understanding of each key risk message.

For statements or questions that use "true" or "yes" vs. "false" or "no" response options, the desired response for the key risk messages is generally "true" or "yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions are formatted to have the respondent disagree with the statement as written by providing response options of "false" or "no" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A). For better readability, the patient questions, only, are presented in the key risk messages tables. Caregiver questions are presented in Appendix A.

Key Risk Message 1: TIRF medicines can cause life-threatening breathing problems that can lead to death.		
Question No.	**Question**	**Desired response**
13	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13d	TIRF medicines can cause life-threatening breathing problems that can lead to death.	**TRUE**

Key Risk Message 2: Patients should not take TIRF medicines if they are not opioid tolerant.		
Question No.	**Question**	**Desired response**
11	Please answer True, False, or I don't know for the following statement:	
	TIRF medicines should only be taken by patients who are opioid tolerant.	**TRUE**
12	Please answer True, False, or I don't know for each of the following statements.	
12a	Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	**TRUE**
13	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13b	It is OK for patients to take TIRF medicines for headache pain.	**FALSE**

Key Risk Message 3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12b	If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.	**TRUE**
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13c	TIRF medicines should be taken exactly as prescribed by the doctor.	**TRUE**
17b	It is OK to take TIRF medicines for short-term pain that will go away in a few days.	**FALSE**

Key Risk Message 4: Patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12c	It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	**FALSE**

Key Risk Message 5: Patients should not give TIRF medicines to anyone else even if they have the same symptoms.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12d	A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	**FALSE**
17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17a	Selling or giving away TIRF medicines is against the law.	**TRUE**

Key Risk Message 6: TIRF medicines should be stored in a safe place away from children and properly disposed.		
Question No.	**Question**	**Desired response**
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13a	TIRF medicines should be stored in a safe place out of the reach of children.	**TRUE**
17c	TIRF medicines must be disposed of as described in the specific product's Medication Guide.	**TRUE**
17e	A TIRF medicine can cause an overdose and death in any child who takes it.	**TRUE**
14	What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)	**Get emergency help right away.**

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4.2.2 Additional Questions

Questions about the requirements of the TIRF REMS, and receipt and understanding of the Medication Guides and PPAF will be asked after the key risk message questions, and will be followed by the collection of demographic information at the completion of the survey.

4.3 Subject Recruitment

Patients will be recruited through a direct letter program. Patients will be invited through a network of national pharmacies and/or a pharmacy benefits management (PBM) partner,

which will provide a broad demographic coverage and include patients in 49 states. Leveraging one or more of these partners, a list will be created of patients who have filled a prescription for a TIRF medicine within 4 months prior to survey launch (first prescriptions and refills). Patients in this list will be invited to participate in the survey through an invitation letter (Appendix B) mailed directly to the patients on the pharmacy or PBM's letterhead at the corporate level via the United States (US) Postal Service.

The invitation will indicate that participants will receive a $50 gift card for completing the survey. Each invitation will also include a unique code and directions for accessing the survey either via the Internet or by telephone through an interviewer at the Survey Coordinating Center. The unique code will be used to identify the manufacturer of the most recent TIRF prescription that the patient filled.

A sample of patients who have filled a prescription for a TIRF medicine within the 4 months prior to survey launch will be chosen from the pharmacy partner's and/or PBM's database. This sampling approach will be used to create several batches of survey invitations. The overall number of unique patients and the duration of the survey period will dictate the size and number of invitation batches. If the required number of completed surveys is not achieved within a reasonable time frame, a second mailing will be sent to non-respondents from the original batch mailing and initial invitations will be sent to patients in the second batch. If the required number of completed surveys is still not achieved within a reasonable time frame, reminder letters will be sent to the patients in the second batch and initial invitations will be sent to the third batch of patients. If these efforts do not result in the required number of surveys within a reasonable time frame, then a new sample of patients may be selected if available. The intervals for sending reminder invitations to non-responders and for selecting a new sample will be condensed as necessary based on the actual rate of survey accrual relative to the proximity of the target survey close date.

All respondents who complete the survey and who provide their contact information will be mailed a $50 gift card to thank them for their participation. The mailing will include a thank you letter, a copy of the product-specific Medication Guide, and a copy of the correct answers to the key risk message questions.

4.3.1 Measures to Minimize Bias in the Sample

The sample of participating patients will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of patients for participation.

Respondents will be offered online or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the online survey or when calling the Survey

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Deleted: Additionally, outbound calls will be placed to prescribers to ask for their support in informing patients about the opportunity to participate in the survey by providing an invitation directly to patients who are prescribed a TIRF medicine A random sample of up to 250 prescribers with at least 5 patients who have filled prescriptions in the 4 months prior to survey implementation will be contacted for this purpose If a prescriber expresses willingness to support the survey effort, an information packet including invitation letters will be mailed to the prescriber Prescribers will not receive any compensation for this support ¶

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Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

5. STUDY POPULATION

5.1.1 Sample Size

A sample of 300 patients treated with TIRF medicines is proposed for the survey wave. The size of the sample was determined based on both practical and statistical considerations. There is no target comprehension rate specified *a priori*. A sample of 300 completed surveys will allow estimation of the comprehension rate for each key risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval	
5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.2 Inclusion Criteria

The following respondents are eligible to participate in the survey:

- Patients who are 18 years of age or older who have filled a prescription for at least one of the TIRF medicines within 4 months prior to survey launch

- Caregivers 18 years of age or older who care for patients who have filled a TIRF medicine prescription within the past 4 months prior to survey launch and are unable to take the survey for themselves

5.1.3 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Patients who have previously participated in the TIRF REMS KAB survey (this exclusion applies to the second and subsequent waves only)

- Patients or their immediate family members who have ever worked for Anesta LLC, Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc.; Par Pharmaceutical, Inc.; Teva Pharmaceuticals, Ltd.; UBC; McKesson Specialty Care Solutions; RelayHealth; or the FDA.

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6. SURVEY PROCESS

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm patient eligibility. The entire survey is expected to take approximately 20 minutes to complete. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, respondents are immediately notified with a thank you message that survey participation has ended. If eligible, respondents are allowed to continue survey participation.

The electronic data capture (EDC) system that is used for both methods of survey administration has been validated and is secure for receiving and storing survey data. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Patient-identifying information will be stored separately from survey data.

6.1.1 Telephone

The telephone survey is facilitated by a trained interviewer from the Survey Coordinating Center using a CATI program. The respondent will be required to provide a unique code to access the survey. Working from a CATI script, the interviewer will read questions or statements to the respondent and enter the responses into the EDC system. Screening and main elements of the questionnaire will be administered sequentially during the same telephone call. Telephone interviewing allows participation of respondents who do not have Internet access, or prefer to complete the survey in this manner.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If respondents select to participate in the survey online, they will be directed to a secured

website and instructed to enter a unique code to access the survey. An Internet survey will be convenient for respondents to participate since they can complete the questionnaire at any convenient time and location during the specified survey time period.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer the survey.

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All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. Any free text fields will be grouped into applicable categories. Verbatim text from open-ended questions will be displayed when appropriate. The following will be reported as part of this analysis:

- The number of invitations issued
- The number of reminder letters
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents who completed all questions presented to them
- Description of survey participants, including:
  - Type of respondent (patient/caregiver)
  - Age (patient/caregiver)
  - Gender (respondent)
  - Educational level (respondent)
  - Main language spoken at home (respondent)

  - Ethnicity (respondent)
  - Race (respondent)
  - Geographic region (respondent)

- Data from all respondents who completed all questions presented to them in the survey ("completers") will be analyzed, including:
  - Frequency distribution of responses to each key risk message question.
  - Percent of completers selecting desired response to each question relating to each key risk message and 95% CI.

Measurement of understanding will be computed for each question of the key risk message individually. A secondary analysis will be conducted to determine the number of completers who answered all items correctly for the key risk message. Behavior questions will be summarized on a question-by-question basis and are not included in the analysis by key risk message.

Additional analyses may be performed as needed.

8. SAFETY EVENT REPORTING

The survey will be conducted via the Internet and by telephone. It is possible that a respondent may report an adverse event or other safety event experienced while taking TIRF medicines either in free text fields of the survey or while in conversation with the Survey Coordinating Center. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. The respondent will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact him/her if there are questions about the survey. The Internet-based questionnaires will be monitored for any comments recorded in free text fields. Information on all comments that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE PSP.

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9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The EDC system used for data collection encrypts all identifiable information and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail a $50 gift card, a Thank You Letter, a product-specific Medication Guide, and correct survey responses to key risk message questions after the survey is completed. Respondent contact information is also requested in the event a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information. A respondent may be contacted only if clarification or follow-up is needed regarding a possible safety event that was mentioned to the interviewer or recorded in free text fields of the online survey.

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to receive TIRF medicines.

This protocol and survey will be reviewed and approved by a central Institutional Review Board (IRB) before administration of the survey.

APPENDIX A Screening and Main Questionnaire

Survey Legend

- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets. **[PATIENT]** indicates text applicable to a patient when it differs from survey text for caregivers, parents and legal guardians. **[PARENT/CAREGIVER/LEGAL GUARDIAN]** indicates text applicable to parents, caregivers, and legal guardians when it differs from survey text for patients.

- **(INTERVIEWER)** is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by tlelphone only (for example, spontaneous adverse event reporting).

- **[ONLINE]** indicates a question is worded specifically for administering the survey online. **[PHONE]** indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.

- **[BEGIN ONLINE/PHONE SURVEY CONTENT]** and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.

- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

  Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.

- **[RANDOMIZE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as “I don’t know,” “Prefer not to answer” or “None of the above” will always appear at the end of the randomized responses.

- **[GO TO Ax]** (Skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

Survey Legend

- **[FREE TEXT]** indicates to the programmer that one line should be provided for data entry.
- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines).

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- **[DROP-DOWN LIST INPUT WITH STATES TABLE]** indicates to the programmer that the response should be a drop-down list containing the states in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

- The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

Northeast Region

- New England Division - ME, NH, VT, MA, RI, CT
- Middle Atlantic Division - NY, NJ, PA

Midwest Region

- East North Central Division - OH, IN, IL, MI, WI
- West North Central Division - MN, IA, MO, ND, SD, NE, KS

South Region

- South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
- East South Central Division - KY, TN, AL, MS

Survey Legend

- West South Central Division - AR, LA, OK, TX

West

- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV
- Pacific Division WA, OR, CA, AK, HI

- The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

[BEGIN SURVEY CONTENT]

[ONLINE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The survey is being conducted by the makers of Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and the generic versions of any of these brands. These are **T**ransmucosal **I**mmediate **R**elease **F**entanyl medicines, also known as rapid onset opioids (and sometimes called "fast acting fentanyls") or TIRF medicines.

The information collected will help the makers of TIRF medicines know if patients and their caregivers understand important information about taking these medicines. The survey will take about 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. Your answers to the questions or your decision to take part in the survey will not affect your ability to receive or take TIRF medicines.

How We Use Your Information

Your answers to the survey questions will be combined with answers given by other people taking the survey. All answers will be put together and reported in anonymous form to manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 gift card for your time.

Your name and address will be used only to send you the gift card, a Thank You Letter, a product-specific Medication Guide, and a copy of the correct answers to key risk message questions, after you complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your answers.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA (Food and Drug Administration) and a company called (b) (4)., which is the Institutional Review Board (IRB) that looks out for the interest of survey participants. Your choice to allow the manufacturers of TIRF medicines to use your information is entirely voluntary, but necessary to take part in this survey.

How to Learn More About This Survey

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If you have questions about the survey, or have any problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297.

If you have questions about your rights as a research participant or related concerns, you may contact the IRB at (b) (4). Be sure to write down this telephone number; it will not be displayed again.

The information in this survey should not take the place of talking with your doctor or health care professional. If you have any questions about your condition or treatment or that of the person you care for, or if you would like more information about TIRF medicines, talk to your doctor, pharmacist, or other health care professional.

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

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Moved up [1]: How to Learn More About This Survey ¶
If you have questions about the survey, or have any problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297 ¶

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[PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The survey is being conducted by the makers of Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and the generic versions of any of these brands. These are Transmucosal Immediate Release Fentanyl medicines, also known as rapid onset opioids **(INTERVIEWER: Please pause briefly)** (and sometimes called "fast acting fentanyls") or TIRF medicines.

(INTERVIEWER: Pronounce "TIRF," then spell out T-I-R-F).

The information collected will help the makers of TIRF medicines know if patients and their caregivers understand important information about taking these medicines. The survey will take about 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. Your answers to the questions or your decision to take part in the survey will not affect your ability to receive or take TIRF medicines.

Now I would like to tell you about how your contact information will be used.

Your answers to the survey questions will be combined with answers given by other people taking the survey. All answers will be put together and reported in anonymous form to manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 gift card for your time.

Your name and address will be used only to send you the gift card, a Thank You Letter, a product-specific Medication Guide, and a copy of the correct answers to key risk message questions, after you complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your answers.

Now I would like to tell you about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA (Food and Drug Administration) and a company called (b) (4)., which is the Institutional Review Board (IRB) that looks out for the interest of survey participants. Your choice to allow the manufacturers of TIRF medicines to use your information is entirely voluntary, but necessary to take part in this survey.

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Once you have answered a question and moved on, you cannot go back and change your answers ¶

If you have questions about your rights as a research participant or related concerns, you may contact the IRB at (b) (4)

The information in this survey should not take the place of talking with your doctor or health care professional. If you have any questions about your condition or treatment or that of the person you care for, or if you would like more information about TIRF medicines, talk to your doctor, pharmacist, or other health care professional.

Please feel free to ask me to repeat any questions or statements as we go through the survey.

Once you have answered a question and moved on, you cannot go back and change your answers.

Moved (insertion) [3]

Thank you for your participation in this survey.

[END PHONE PREAMBLE 1]

1. Do you agree to take part in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Within the last 4 months, have you filled a prescription for yourself for a transmucosal immediate release fentanyl medicine (known as "TIRF medicines")? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of any of these brands.

   - ○ Yes **[GO TO Q4]**
   - ○ No
   - ○ I don't know

3. Are you a caregiver for someone who has filled a prescription for a TIRF medicine within the last 4 months? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and the generic versions of any of these brands.

   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

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4. **[PATIENT]** For which TIRF medicines have you filled a prescription in the last 4 months? Please select all that apply.

[CAREGIVER] For which TIRF medicines has the person you care for filled a prescription in the last 4 months? Please select all that apply.

- ☐ Abstral
- ☐ Actiq, including generic versions of Actiq
- ☐ Fentora
- ☐ Lazanda
- ☐ Onsolis
- ☐ Subsys
- ☐ Other
- ☐ I don't know **[CLEAR ALL OTHER SELECTIONS]**

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5. Have you ever taken part in a survey about a TIRF medicine before?

- ○ Yes **[TERMINATE]**
- ○ No
- ○ I don't know **[TERMINATE]**

6. Which of the following groups best describes your age?

- ○ Under 18 **[TERMINATE]**
- ○ 18 – 29
- ○ 30 – 39
- ○ 40 – 49
- ○ 50 – 59
- ○ 60 – 69
- ○ 70 or older
- ○ Prefer not to answer **[TERMINATE]**

7. **[CAREGIVER ONLY]** Which of the following groups best describes the patient's age?

- ○ Under 16
- ○ 16 – 29
- ○ 30 – 39
- ○ 40 – 49
- ○ 50 – 59
- ○ 60 – 69
- ○ 70 or older
- ○ Prefer not to answer **[TERMINATE]**

8. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

- ☐ Anesta LLC **[TERMINATE]**
- ☐ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**
- ☐ Depomed, Inc. **[TERMINATE]**
- ☐ Galena Biopharma, Inc. **[TERMINATE]**
- ☐ Insys Therapeutics **[TERMINATE]**
- ☐ Mallinckrodt Pharmaceuticals **[TERMINATE]**
- ☐ McKesson Specialty Care Solutions **[TERMINATE]**
- ☐ Meda Pharmaceuticals **[TERMINATE]**
- ☐ Mylan, Inc. **[TERMINATE]**
- ☐ Par Pharmaceutical, Inc. **[TERMINATE]**
- ☐ RelayHealth**[TERMINATE]**
- ☐ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- ☐ United BioSource Corporation **[TERMINATE]**
- ☐ FDA (Food and Drug Administration) **[TERMINATE]**
- ☐ No **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- ☐ I don't know **[TERMINATE]**

[PREAMBLE 2]

[PATIENT]Please answer the following questions based on information about the TIRF medicine that was most recently prescribed for you. TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands. Please think of the information that you read or that was provided to you by a doctor, nurse, or other healthcare professional. If you don't know the answers to any of the following questions please respond "I don't know" instead of guessing the correct responses.

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[CAREGIVER]Please answer the following questions based on information about the TIRF medicine that was most recently prescribed for the patient. TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands. Please think of the information that you read or that was provided to you or to the patient by a doctor, nurse, or other healthcare professional. If you don't know the answers to any of the following questions please respond "I don't know" instead of guessing the correct responses.

9. [PATIENT] Did the doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed for you? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands.

   [CAREGIVER] Did the doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed to the patient? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands.

   - ○ Yes
   - ○ No
   - ○ I don't know

10. [PATIENT] For which of the following conditions should you use a TIRF medicine?

    [CAREGIVER] For which of the following conditions should the person you take care of use a TIRF medicine?

[RANDOMIZE LIST]	Yes	No	I don't know
10a. Headache or migraine pain	○	○	○
10b. Breakthrough pain from cancer	○	○	○
10c. Dental pain	○	○	○
10d. Pain after surgery	○	○	○
10e. Long-lasting painful conditions not caused by cancer	○	○	○

11. Please answer True, False, or I don't know for the following statement:

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TIRF medicines should only be taken by patients who are opioid tolerant.

- ○ True
- ○ False
- ○ I don't know

12. Please answer True, False, or I don't know for each of the following statements.

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
12a.	Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	○	○	○
12b.	If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.	○	○	○
12c.	It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	○	○	○
12d.	A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	○	○	○

13. **[PATIENT]** Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.

[CAREGIVER] Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for the patient.

[RANDOMIZE LIST]	**True**	**False**	**I don't know**
13a. TIRF medicines should be stored in a safe place out of the reach of children.	○	○	○
13b. It is OK for patients to take TIRF medicines for headache pain.	○	○	○
13c. TIRF medicines should be taken exactly as prescribed by the doctor.	○	○	○
13d. TIRF medicines can cause life-threatening breathing problems that can lead to death.	○	○	○

14. What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)

[RANDOMIZE LIST]

- ○ Wait an hour and see if the person is OK.
- ○ Get emergency help right away.
- ○ Do nothing.
- ○ I don't know.

15. **[PATIENT]** Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for you?

[CAREGIVER] Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for the patient?

- o Yes
- o No
- o I don't know

16. **[PATIENT]** Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for you?

[CAREGIVER] Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for the patient?

- o Yes
- o No
- o I don't know

17. **[PATIENT]** Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.

[CAREGIVER] Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for the patient.

[RANDOMIZE LIST]	**True**	**False**	**I don't know**
17a. Selling or giving away TIRF medicines is against the law.	○	○	○
17b. It is OK to take TIRF medicines for short-term pain that will go away in a few days.	○	○	○
17c. TIRF medicines must be disposed of as described in the specific product's Medication Guide.	○	○	○
17d. TIRF medicines are only available to patients through a pharmacy enrolled in a special program (called the TIRF REMS Access Program).	○	○	○
17e. A TIRF medicine can cause an overdose and death in any child who takes it.	○	○	○

[PREAMBLE 3]

[PATIENT] The next set of questions is about the Medication Guide for the TIRF medicine that was most recently prescribed for you.

[CAREGIVER] The next set of questions is about the Medication Guide for the TIRF medicine that was most recently prescribed for the patient.

[BOTH] A Medication Guide is a paper handout that contains important information about the risks associated with the use of a TIRF medicine and how to use it safely. Medication Guides always include the title "Medication Guide" followed by the name of the medicine and its pronunciation. The Medication Guide usually has a section titled "What is the most important information I should know?" The Medication Guide is in a question-and-answer format and may be given to you by your pharmacist, doctor, or other healthcare professional.

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Deleted: [END PREAMBLE 3]¶

18. **[PATIENT]** Have you ever received a Medication Guide for the TIRF medicine that was prescribed for you?

[CAREGIVER] Have you or the patient ever received a Medication Guide for the TIRF medicine that was prescribed for the patient?

- ○ Yes
- ○ No **[GO TO PREAMBLE 4]**
- ○ I don't know **[GO TO PREAMBLE 4]**

19. **[PATIENT]** Did you receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?

[CAREGIVER] Did you or the patient receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?

- ○ Yes
- ○ No **[GO TO Q21]**
- ○ I don't know **[GO TO Q21]**

20. **[PATIENT]** When was the Medication Guide given to you? Please select all that apply.

[CAREGIVER] When was the Medication Guide given to you or the patient? Please select all that apply.

- ☐ At the first appointment with the doctor who prescribed the TIRF medicine
- ☐ At the last appointment with the doctor who prescribed the TIRF medicine
- ☐ I don't remember **[CLEAR ALL OTHER SELECTIONS]**

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21. **[PATIENT]** Did you receive the Medication Guide for the TIRF medicine from the pharmacy?

[CAREGIVER] Did you or the patient receive the Medication Guide for the TIRF medicine from the pharmacy?

- ○ Yes
- ○ No **[GO TO Q23]**
- ○ I don't know **[GO TO Q23]**

22. **[PATIENT]** How frequently do you receive a Medication Guide for the TIRF medicine at the pharmacy?

[CAREGIVER] How frequently do you or the patient receive a Medication Guide for the TIRF medicine at the pharmacy?

- ○ Only with the first filled prescription
- ○ Each time a prescription is filled
- ○ Other (please specify): _____
- ○ I don't know

23. Did you read the Medication Guide?

- ○ Yes
- ○ No **[GO TO Q26]**
- ○ I don't know **[GO TO Q26]**

24. How much did you read?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ I don't know

25. How much of the Medication Guide did you understand?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ None of it
- ○ I don't know

26. Did someone offer to explain the Medication Guide to you?

- ○ Yes
- ○ No **[GO TO Q30]**
- ○ I don't know **[GO TO Q30]**

27. Who offered to explain the Medication Guide to you? Please select all that apply

- ☐ The doctor or another healthcare professional in the doctor's office
- ☐ The pharmacist where the TIRF medicine prescription was filled
- ☐ Someone else (specify the type of person but not his/her name)

[FREE TEXT]

Deleted: (Select

Deleted:)

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_____

28. Did you accept the offer to have the Medication Guide explained to you?

- ○ Yes
- ○ No **[GO TO Q30]**
- ○ I don't know **[GO TO Q30]**

29. How much of the explanation did you understand?

- All of it
- Most of it
- Some of it
- None of it
- I don't know

30. Did you or do you have any questions about the information in the Medication Guide?

- Yes
- No **[GO TO PREAMBLE 4]**
- I don't know **[GO TO PREAMBLE 4]**

31. What are your questions? **[MULTILINE INPUT]**

[PREAMBLE 4]

The next set of questions is about the Patient-Prescriber Agreement Form for TIRF medicines. As a reminder, TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of any of these brands. The Patient-Prescriber Agreement is a form that is signed by the doctor and the patient or their caregiver. This form may also be referred to as the Prescriber-Patient Agreement.

[END PREAMBLE 4]

32. Did the doctor or someone in the doctor's office explain the Patient-Prescriber Agreement Form to you?

- Yes
- No **[GO TO Q34]**
- I don't know **[GO TO Q34]**

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33. How much of the explanation did you understand?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ None of it
- ○ I don't know

34. **[PATIENT]** Did you sign a Patient-Prescriber Agreement Form?

[CAREGIVER] Did you or the person you are caring for sign a Patient-Prescriber Agreement Form?

- ○ Yes
- ○ No **[GO TO DEMOGRAPHICS PREAMBLE]**
- ○ I don't know **[GO TO DEMOGRAPHICS PREAMBLE]**

35. Did the doctor or someone in the doctor's office give you a copy of the signed Patient-Prescriber Agreement Form?

- ○ Yes
- ○ No
- ○ I don't know

[DEMOGRAPHICS PREAMBLE]

There are just a few more questions to help us combine your answers with other answers we have received.

36. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

37. What is the highest level of education you have completed?

- ○ Less than high school
- ○ Some high school
- ○ High school graduate/GED
- ○ Some college/Associate's degree
- ○ Bachelor's degree
- ○ Master's degree
- ○ Professional or Doctoral degree
- ○ Prefer not to answer

38. What is the main language you speak at home?

Deleted: (Please select only one)

- ○ English
- ○ French
- ○ Spanish
- ○ Portuguese
- ○ Italian
- ○ German
- ○ Chinese
- ○ Japanese
- ○ Korean
- ○ Other
- ○ Prefer not to answer

39. Are you Hispanic or Latino?

- ○ Yes
- ○ No
- ○ Prefer not to answer

40. For informational purposes only, which of the following U.S. census categories best describes your race?

Deleted: (Please select only one)

- ○ American Indian or Alaska Native
- ○ Asian (origins of Far East, Southeast Asia or the Indian subcontinent)
- ○ Black or African American
- ○ Native Hawaiian or Other Pacific Islander
- ○ White
- ○ Two or more races
- ○ Other
- ○ Prefer not to answer

41. In which state do you live?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" AT END]

[PHONE ONLY: ADVERSE EVENT/PRODUCT COMPLAINT]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- Yes
- No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[CLOSING 1]

You are eligible to receive a $50 gift card for your time completing the survey. In order to receive the gift card, we need to collect your name and address so that we can mail it to you. If you do not provide your name and address you will not receive the gift card for your time taking the survey.

Do you agree to give us your name and mailing address so we can send your payment?

- Yes
- No **[SKIP TO CLOSING 2]**

FIRST NAME: **[FREE TEXT]**

LAST NAME: **[FREE TEXT]**

ADDRESS: **[MULTILINE INPUT]**

CITY: **[FREE TEXT]**

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: **[5 NUMERIC CHARACTERS ONLY]**

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[CLOSING 2]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

Do you want to provide your telephone number?

- ○ Yes
- ○ No **[SKIP TO CLOSING 3]**

Telephone: **[10-DIGIT NUMERIC CHARACTERS]**

[END CLOSING 2]

[CLOSING 3]

This is the end of the survey. If you have questions about the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Thank you again for your help.

[END OF SURVEY CONTENT]

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APPENDIX B SAMPLE Patient Letter of Invitation

[PAT_FIRST_NAME] [PAT_LAST_NAME
[CURR_DATE]
[PAT_STREET_ADDR]
[PAT_CITY], [PAT_STATE] [PAT_ZIP]

Dear [PAT_FULL_NAME]:

Thank you for choosing [pharmacy partner or PBM name] for your prescription needs. The purpose of this letter is to inform you about a voluntary research survey being conducted by [COMPANY], the maker of [BRAND_GENERIC]. The survey is part of an FDA requirement to find out if patients and/or their caregivers understand important safety information about [BRAND] and other medicines like it. The first 300 people who complete this 20-minute survey and provide their contact information will receive a $50 [pharmacy partner or PBM name] gift card from [COMPANY] to thank them for their time.

You may be eligible to take part if you have taken [BRAND] and are 18 years of age or older. If you are unable to take the survey yourself, a caregiver who is 18 or older may be eligible to take the survey for you. The survey asks questions about the type of information you received about [BRAND] and where you get your medical information.

If you are interested in participating and to find out if you are eligible:

- Go to www.TIRFREMSsurvey.com any time or
- Call 877-379-3297, 8 a.m. to 8 p.m. Eastern Time, Monday through Friday

Please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**.

It is recommended that you take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.

(over, please)

You are not required to take part in this survey. If you choose to take part, please be assured that your contact information and your individual responses will be kept strictly confidential. You will not be asked to identify yourself to participate in the survey. However, if you wish to receive the $50 gift card from [COMPANY], you must provide your name and contact information for delivery. Your answers to the survey questions will be combined with answers given by others, and your name will not be used in any written report or publication. Neither taking the survey nor your answers to the questions will affect your ability to receive or take [BRAND].

Sincerely,

[Pharmacy partner or PBM name]

[COMPANY] funded the cost of the gift card, the cost of mailing this letter and paid a fee to [pharmacy partner or PBM name]. The research study is not being conducted by [pharmacy partner or PBM name]. No information that can identify you, your medication, or your health condition will be provided by [pharmacy partner or PBM name] to [COMPANY]. This letter provides information about a drug prescribed by your doctor and is not a recommendation by [pharmacy partner or PBM name] to use a particular drug for your condition. Call [pharmacy partner or PBM name] toll free at xxx-xxx-xxxx if you do not wish to continue receiving mailings about [BRAND] from [pharmacy partner or PBM name].

12.4.2 Pharmacy KAB Survey

Title:	**Transmucosal Immediate Release Fentanyl (TIRF) REMS Assessment** **Quantitative Testing of Pharmacist Knowledge, Attitudes, and Behavior (KAB) about TIRF Products' Safety and Use Information**
Document Number	Wave 3, 36-month REMS Assessment; Version 1.0
Survey Time Period	18 August 2014 – 22 October 2014
Product Name:	Transmucosal Immediate Release Fentanyl
Sponsor:	**TIRF REMS Industry Group (TRIG) of Companies:** Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc. Galena Biopharma, Inc. Insys Therapeutics Mallinckrodt Pharmaceuticals Meda Pharmaceuticals Mylan, Inc. Par Pharmaceutical, Inc.
Date:	19 December 2014

Confidentiality Statement

TABLE OF CONTENTS **PAGE**

TABLE OF CONTENTS 2
LIST OF TABLES 3
LIST OF APPENDICES 4
LIST OF ABBREVIATIONS 5
1. PHARMACIST SURVEY BACKGROUND 6
2. PHARMACIST SURVEY OBJECTIVES 7
3. SURVEY METHODOLOGY 7
3.1 Survey Sample 7
3.1.1 Eligibility 8
3.1.2 Recruitment 8
3.2 Questions and Statements on Key Risk Messages 8
3.2.1 Key Risk Message 1 9
3.2.2 Key Risk Message 2 9
3.2.3 Key Risk Message 3 10
3.2.4 Key Risk Message 4 11
3.3 Additional Questions 11
4. STATISTICAL METHODS 12
4.1 Study Population 12
4.1.1 Primary Analysis Population 12
4.1.2 Sub-groups of Interest 12
4.1.2.1 Primary Analyses 13
4.1.2.2 Secondary Analyses 13
4.1.3 Pharmacist Report of an Adverse Event, Product Complaint, or Medical Information Request during the Survey 13
5. RESULTS 14
5.1 Survey Participants 14
5.1.1 Survey Participant Administration Results 14
5.1.2 Pharmacist Demographic and TIRF Product Dispensing Characteristics 18

5.1.3 TIRF Medicines Educational Materials 21
5.2 KAB Survey Objectives 22
5.2.1 Key Risk Message Results 22
5.2.1.1 Key Risk Message 1 22
5.2.1.2 Key Risk Message 2 25
5.2.1.3 Key Risk Message 3 27
5.2.1.4 Key Risk Message 4 29
5.2.2 Other Survey Questions 31
5.2.2.1 Additional Questions about TIRF Medicines Safety 31
5.2.2.2 Pharmacist Activities When Dispensing TIRF Medicines 34
5.2.3 Sub-group Analysis of Responses to Key Risk Messages 38
5.3 Spontaneous Reporting of Adverse Events, Product Complaints, or Medical Information Requests 38
5.4 Summary of Correct Responses for Key Risk Messages 39
6. FDA FEEDBACK 44
7. DISCUSSION AND CONCLUSIONS 44

LIST OF TABLES

Table 1. Survey Participant Administration Results 14
Table 2. Survey Participant Screening Results 16
Table 3. Time to Complete Survey for Completers (Minutes) 17
Table 4. Demographic Characteristics of Eligible Pharmacists 19
Table 5. Characteristics of Respondents Completing the Survey 20
Table 6. Responses to Questions About TIRF Medicines Educational Materials 21
Table 7. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients 23
Table 8. Responses Linked to Key Risk Message 2: TIRF Medicines Are Only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (16 Years of Age and Older for Actiq® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain 26

Table 9. Responses Linked to Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist and a Schedule II Controlled Substance, With Abuse Liability Similar to Other Opioid Analgesics. 28
Table 10. Responses Linked to Key Risk Message 4: TIRF Medicines Are Not Interchangeable with Each Other, Regardless of Route of Administration. 30
Table 11. Responses to Additional Questions about the Safe Use of TIRF Medicines 31
Table 12. Responses to Additional Questions about the Safe Use of TIRF Medicines: Question asked of Inpatient Pharmacists, Only 34
Table 13. Responses to Questions about Activities When Dispensing TIRF Medicines 35
Table 14. Responses to All Questions about Activities When Dispensing TIRF Medicines: Asked of Inpatient Pharmacies Only 37
Table 15. Responses to All Questions about Activities When Dispensing TIRF Medicines: Outpatient Pharmacists Only 37
Table 16. Responses to All Questions about Activities When Dispensing TIRF Medicines: Closed System Pharmacy Outpatient Pharmacists Only 38
Table 17. Summary of Correct Responses for Key Risk Messages 40
Table 18. Correct/Desired Response Rate of Low Scoring Questions Across the Three Pharmacist KAB Survey Waves. 45

LIST OF APPENDICES

Appendix A Pharmacy Survey Protocol 48
Appendix B Pharmacy Survey Listings and Sub-group Analysis Tables 49
Appendix C Pharmacy Survey Protocol Track Change Document: Comparison of 24-month Survey to 36-month Survey 50

LIST OF ABBREVIATIONS

AE/PC PSP	Adverse Event/Product Complaint Project Specific Procedure
CSP	Closed System Pharmacy
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
KAB	Knowledge, Attitudes, and Behavior
NA	Not Applicable
REMS	Risk Evaluation and Mitigation Strategy
SD	Standard Deviation
SCC	Survey Coordinating Center
TIRF	Transmucosal Immediate Release Fentanyl
TIRF medicines	Transmucosal Immediate Release Fentanyl products
TIRF REMS Access Program	REMS Program for TIRF medicines
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States
USPS	United States Postal Service

1. PHARMACIST SURVEY BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines are a class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® [fentanyl citrate oral transmucosal lozenge] and equivalent generics) who are receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and their generic equivalents. The TIRF Risk Evaluation and Mitigation Strategy (REMS) Industry Group (TRIG) includes Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.), Depomed, Inc., Galena Biopharma, Inc., Insys Therapeutics, Mallinckrodt Pharmaceuticals, Meda Pharmaceuticals, Mylan, Inc., and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a shared system REMS is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on 28 December 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by the following:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

2. Preventing inappropriate conversion between TIRF medicines.

3. Preventing accidental exposure to children and others for whom it was not prescribed.

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess pharmacists' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS educational materials, enrollment form, and Prescribing Information of each product. Administration of the surveys conducted among pharmacies enrolled in the TIRF REMS Access Program is described in the protocol (See Appendix A). Note: Protocol and Survey question revisions from the 24-month assessment report are identified in the track change version found in Appendix C.

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

This report describes the results from the pharmacists survey conducted for the 36-month TIRF REMS Access Program Assessment. The 36-month Knowledge, Attitudes, and Behavior (KAB) survey launched on 18 August 2014 and closed on 22 October 2014.

2. PHARMACIST SURVEY OBJECTIVES

The evaluation survey uses a questionnaire to document the level of knowledge and assess the attitudes and behavior of pharmacists regarding the following key information and risk messages communicated through the REMS:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.

2. TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 or older for Actiq® and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

3. TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.

4. TIRF medicines are not interchangeable with each other, regardless of route of administration.

5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey also collects data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

3. SURVEY METHODOLOGY

This section summarizes the survey design and the questions that were designed to test pharmacist understanding of the key risk messages of the REMS. Full details of the survey design are in the protocol, which can be found in Appendix A.

3.1 Survey Sample

This survey was conducted among a random sample of pharmacists who were enrolled in the TIRF REMS Access Program as of 05 August 2014. A target sample of 300 pharmacists who dispense TIRF products and were known to have received the REMS educational materials were surveyed in this third KAB survey conducted from 18 August 2014 to 22 October 2014. The size of the sample was determined on both practical and statistical considerations. The survey was written to reflect wording for both methods of survey administration: Internet-based and telephone.

3.1.1 Eligibility

Subjects were recruited from a random sample of pharmacists from pharmacies that were enrolled in the TIRF REMS Access Program. Any pharmacist who worked at an enrolled pharmacy was eligible to participate. Respondents or respondents with immediate family members who had ever worked for any of the TRIG companies, McKesson Specialty Care Solutions, RelayHealth, United BioSource Corporation (UBC), or the FDA were not eligible to participate.

Respondents who participated in the previous waves of the survey (12-month TIRF REMS Access Program Assessment or the 24-month TIRF REMS Access Program Assessment) were not eligible to participate.

3.1.2 Recruitment

Subjects were recruited via invitation letter sent through the United States Postal Service (USPS) or via fax (see Section 5.1.1 for more detail).

The required number of completed surveys was not achieved within approximately 10 days after the first mailing; thus additional mailings were distributed to non-respondents from the original sample to maximize participation.

Each letter of invitation included a unique code needed to complete the survey. There were three categories of pharmacies which were sampled: Closed System Pharmacy (CSP), Inpatient Pharmacy, and Outpatient Pharmacy. Each type of pharmacy was provided with a unique access code since some questions in the survey were specific to only one type of pharmacy. The code was deactivated after the respondent had initiated the survey (whether or not the survey was completed).

Pharmacists were given the option of taking the survey by telephone via the Survey Coordinating Center (SCC) or online via a secure website. All participating pharmacists were offered an honorarium of $50 for a completed survey. The survey was estimated to take approximately 20 minutes to complete.

3.2 Questions and Statements on Key Risk Messages

The questions and statements comprising the knowledge survey were constructed to test the pharmacists' understanding of the key risk messages of the REMS. The questions were to be answered either by selecting options from multiple-choice lists that include statements of the specific key risk messages or by choosing "Yes" or "True," "No" or "False," or "I Don't Know" regarding statements about TIRF medicines.

For statements or questions that had "True" or "Yes" vs. "False" or "No" response options, the desired response for key risk messages was generally "True" or "Yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions were formatted to have the respondent disagree with the statement as written by providing response options of "False" or "No" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

3.2.1 Key Risk Message 1

Key Risk Message 1 referred to the pharmacist's knowledge of the specific contraindications for TIRF medicines in opioid non-tolerant patients.

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired response**
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a	Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer	***True***
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before	***False***
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	***False***
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	***True***
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	***True***
7c	TIRF medicines may be used in opioid non-tolerant patients.	***False***
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	***True***

3.2.2 Key Risk Message 2

Key Risk Message 2 referred to the pharmacist's knowledge of the indications for prescribing TIRF medicines for the management of breakthrough pain in opioid-tolerant adult cancer patients.

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.		
Question No.	**Question**	**Desired response**
9	Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a	Acute or postoperative pain	***No***
9b	Headache or migraine pain	***No***
9c	Dental pain	***No***
9d	Breakthrough pain from cancer	***Yes***
9e	Chronic non-cancer pain	***No***

3.2.3 Key Risk Message 3

Key Risk Message 3 referred to the pharmacist's knowledge of the risk factors and signs and symptoms of opioid abuse in patients who take TIRF medicines.

Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.		
Question No.	**Question**	**Desired response**
7	Please answer True, False, or I don't know for each statement about TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	***True***
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a	A personal history of psychiatric illness	***Yes***
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	***Yes***
10	Please answer True, False, or I don't know for each statement about TIRF medicines.	
10a	TIRF medicines can be abused in a manner similar to other opioid agonists.	***True***

3.2.4 Key Risk Message 4

Key Risk Message 4 referred to the pharmacist's knowledge of the interchangeability of TIRF medicines based on route of administration, pharmacokinetic absorption, and dosage.

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired response**
10	Please answer True, False, or I don't know for each statement about TIRF medicines.	
10b	TIRF medicines are interchangeable with each other regardless of route of administration.	***False***
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	***True***
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	***True***

3.3 Additional Questions

The survey also contained questions (Question 12a-f) about the requirements of the TIRF REMS Access Program and receipt and understanding of the TIRF educational materials. The following questions about behaviors were asked after the key risk message questions:

Question No.	**Question**
12	How frequently do you perform the following activities when dispensing TIRF medicines?
12a	Ask patients (or their caregivers) about the presence of children in the home
12b	Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
12c	Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
12d	Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
12e	Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
12f	Give patients (or their caregivers) the Medication Guide for their TIRF medicine

4. STATISTICAL METHODS

4.1 Study Population

4.1.1 Primary Analysis Population

The primary population for analysis was all eligible pharmacists who completed the survey. Eligible pharmacists were defined as those respondents who answered ***Yes*** to Question 1 (agree to take part in survey), and to Question 3 (work at a pharmacy that is enrolled in the TIRF REMs Access Program), and ***No*** to Question 2 (participated in past survey) and Question 4 (worked for a TRIG company, UBC, or FDA). A completed survey was a survey in which all non-eligibility questions as appropriate were answered. Some questions may not have been answered because of skip logic in the survey questionnaire.

4.1.2 Sub-groups of Interest

The following sub-group analyses of responses to key risk messages were conducted when the sub-group included at least 20 respondents. Of note, sub-group analysis 3 was not done since only 13 pharmacists completed the survey via telephone.

Sub-group analysis 1: Reading Medication Guide or Full Prescribing Information (Questions 18, 19, 20 and 21):

- S-1a - Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).
- S-1b - Respondents who responded No or I don't know to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.

Sub-group analysis 2: Time to complete survey - Internet:

- S-2a - <10 min
- S-2b - 10 to <20 min
- S-2c - ≥20 min

Sub-group analysis 3: Time to complete survey: Telephone

- S-2a - <10 min
- S-2b - 10 to <20 min
- S-2c - ≥20 min

Sub-group analysis 4: Modality to complete survey:

- S-4a - Internet
- S-4b – Telephone

Sub-group analysis 5: Time practicing as a pharmacist (Question 28):

- S-5a - Less than 3 years
- S-5b - 3 to 5 years
- S-5c - 6 to 15 years
- S-5d - More than 15 years

Sub-group analysis 6: Number of times per month dispensed TIRF medicines within the last 6 months (Question 25):

- S-6a - None
- S-6b - 1 - 2 times per month
- S-6c - 3 - 5 times per month
- S-6d - More than 5 times per month

Results of sub-group analyses performed are provided in Appendix B.

4.1.2.1 Primary Analyses

Primary analyses were done for all key risk messages. The primary analysis for a key risk message evaluated the number and percentage of correct responses for each individual question/component defined by the key risk message. The correct response to each question/component was identified in the body of the risk message table (Section 3.3).

4.1.2.2 Secondary Analyses

Secondary analyses evaluated the number and percentages of correct responses and the average number of correct responses within the risk message overall to assess understanding of the comprehensive key risk message. A correct response rate of 65% or greater was considered to represent adequate understanding of each concept or key risk message.

4.1.3 Pharmacist Report of an Adverse Event, Product Complaint, or Medical Information Request during the Survey

A pharmacist may have reported an adverse event or other event experienced by a patient while taking a TIRF product either in free text fields while taking the online survey or while in conversation with the SCC Associate. If an event was mentioned to the SCC Associate, the Associate documented the event or complaint, the verbatim response, and the pharmacist's contact information, if provided. The pharmacist was also informed that a representative from the appropriate TIRF medicine sponsor may contact them to obtain additional information about the event. The Internet surveys were monitored for any comments recorded in the free text field. Information on all reports (Internet or telephone) that constituted an adverse event or other event was forwarded to the appropriate TIRF medicine sponsor for processing within 1 business day of awareness of the event as outlined in the Adverse Event/Product Complaint Project Specific Procedure (AE/PC PSP).

5. RESULTS

Results of the pharmacist responses to questions in the KAB survey are summarized in this section and a full set of responses can be found in Appendix B.

5.1 Survey Participants

5.1.1 Survey Participant Administration Results

A total of 4,022 pharmacists were invited to participate in this survey (Table 1). Of those invited to participate, 2625 were outpatient pharmacists, 1,056 were inpatient pharmacists, and 341 were pharmacists practicing in CSPs. An additional 9,051 reminder letters were sent in six separate mailings. Most pharmacists may have received more than 1 reminder letter. There were no duplicate surveys. Note: Once the target number of 300 completed surveys was achieved the survey was closed.

From the total of 404 respondents who agreed to participate in the survey, 300 pharmacists met eligibility criteria and completed the survey. Of these 300 pharmacists, 287 (95.7%) completed the survey online, and 13 (4.3%) completed it by telephone. Of the 300 pharmacists who completed the survey, 1 was a CSP pharmacist, 15 were inpatient pharmacists, and 284 were outpatient pharmacists (see Table 14, Table 15, and Table 16).

Table 1. Survey Participant Administration Results

Summary Statistic	Screened Pharmacists N=404[1]	
	All Respondents	
	N	%
Number of invitations issued to pharmacists	4022	
Number of reminder letters issued to pharmacists	9051	
Number of pharmacists screened for participation	404[1]	
Number of pharmacists eligible for participation	300[2]	74.3
Number of screened pharmacists eligible for participation who answered all questions presented to them	300	100.00

Table 1. Survey Participant Administration Results

Summary Statistic	Screened Pharmacists N=404[1]	
	All Respondents	
	N	%
Method of Survey Completion		
Number of surveys completed by telephone	13	4.3[3]
Number of surveys completed by Internet	287	95.7[3]

[1] The denominator for the percentage of eligible pharmacists is the number of screened pharmacists (N=404).

[2] The denominator for percentages of eligible pharmacists completing the survey is the number of eligible pharmacists (N=300)

3 The denominator for percentages completed by telephone or Internet is the number of eligible pharmacists who completed the survey. (N=300).

As shown in Table 2, a total of 404 pharmacists agreed to participate in this survey. During the screening process it was determined 104 respondents (25.7%) were not eligible to participate in the survey because they either indicated they had participated in or did not know whether they participated in a survey about TIRF medicines before, worked in pharmacies that were not enrolled or they did not know whether their pharmacy was enrolled in the TIRF REMSor indicated they, or an immediate family member, had worked for a TRIG company, UBC, or FDA in the past or the respondent did not know if they or an immediate family member had worked for a TRIG company, UBC, or FDA in the past. . Thus, there were 300 eligible participants, all of whom completed the survey (Table 2).

Table 2. Survey Participant Screening Results

Question	Screened Pharmacists N=404		Eligible Completed Pharmacists N=300	
	n	%	n	%
Question 1: Do you agree to participate in this survey?				
Yes	404	100.0	300	100.0
No[1]	0	0.0		
Question 2: Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and generic versions of any of these brands				
Yes[1]	18	4.5		
No	336	83.2	300	100.0
I don't know[1]	50	12.4		
Question not asked[2]	0	0.0		
Question 3: Do you work in a pharmacy that is enrolled in the TIRF REMS Access Program?				
Yes	306	75.7	300	100.0
No[1]	8	2.0		
I don't know[1]	22	5.4		
Question not asked[2]	68	16.8		
Question 4: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.[3]				
Anesta LLC.[1]	1	0.2		
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)[1]	1	0.2		
Depomed, Inc.[1]	1	0.2		
Galena Biopharma[1]	1	0.2		
Insys Therapeutics[1]	1	0.2		
Mallinckrodt Pharmaceuticals[1]	1	0.2		
McKesson Specialty Care Solutions[1]	1	0.2		
Meda Pharmaceuticals[1]	1	0.2		
Mylan Inc.[1]	1	0.2		
Par Pharmaceutical, Inc.[1]	1	0.2		
RelayHealth[1]	1	0.2		

Table 2. Survey Participant Screening Results

Question	Screened Pharmacists N=404		Eligible Completed Pharmacists N=300	
	n	%	n	%
Teva Pharmaceuticals, Ltd.[1]	2	0.5		
United BioSource Corporation[1]	1	0.2		
FDA[1]	1	0.2		
None of these apply[4]	301	74.5	300	100.0
I don't know[1]	4	1.0		
Prefer not to answer[1]	0	0.0		
Question not asked[2]	98	24.3		

[1] Ineligible to participate in the survey.
[2] Question not asked due to previous question elimination.
[3] More than one response can be selected, so percentages may not sum to 100%.
[4] Ineligible if selected in addition to another response.

Pharmacists taking the survey online took an average of 13.5 minutes to complete it, while those taking it by telephone took an average of 18.6 minutes (Table 3).

Table 3. Time to Complete Survey for Completers (Minutes)

Summary Statistic	Telephone	Internet	Total[1]
N	13	287	300
Mean (± SD)	18.6 (3.94)	13.5 (7.33)	13.8 (7.29)
Minimum	14	4	4
Median	18.0	11.5	11.9
Maximum	28	60	60
Category			
0 – <5 Minutes	0	4	4
5 – <10 Minutes	0	106	106
10 – <15 Minutes	1	94	95
15 – <20 Minutes	8	40	48
20 – <25 Minutes	3	21	24
25 – <30 Minutes	1	10	11
30 Minutes or More	0	12	12

[1] Number of eligible pharmacists completing the survey (See Table 1).
SD = Standard Deviation

5.1.2 Pharmacist Demographic and TIRF Product Dispensing Characteristics

The demographic characteristics of pharmacists who completed the survey are shown in Table 4, and their experience with prescribing TIRF medicines is summarized in Table 5.

The majority of pharmacists who completed the survey were male (186, 62.0%), and out of 300 eligible pharmacists, 202 (67.3%) had been a practicing pharmacist for 11 or more years. Respondents from the South, Northeast, and Midwest reflected 37.7%, 27.7%, and 20.3% of total respondents, respectively, while respondents from the Western region of the United States (US) composed 14.3% of total respondents. There were no respondents from Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam identified as "Other" in Table 4 below.

Most pharmacists (230, 76.7%) functioned as the pharmacist-in-charge for the TIRF REMS Access Program where they worked. Note: FDA feedback received in August 2014 recommended that in future pharmacist surveys to consider including a higher percentage of non-supervisory dispensing pharmacists; this will be addressed in the 48-month Pharmacist KAB report. The majority of pharmacists (213, 71.0%) had dispensed a TIRF medicine zero to 2 times per month within the past 6 months. The most frequently dispensed TIRF medicine within the 6 months prior to taking the survey was Actiq® or generic Actiq® (127/168 pharmacists, 75.6%). Note: Two pharmacists indicated that they dispensed Onsolis® during the 6 months prior to taking the survey. However, Onsolis® was not available to any pharmacy at that time. Onsolis® was last available in May 2011.

Table 4. Demographic Characteristics of Eligible Pharmacists

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
Question 27: What is your gender?		
Male	186	62.0
Female	108	36.0
Prefer not to answer	6	2.0
Question 28: In total, how many years have you been a practicing pharmacist?		
Less than 3 years	16	5.3
3-5 years	28	9.3
6-10 years	50	16.7
11-15 years	52	17.3
More than 15 years	150	50.0
Prefer not to answer	4	1.3
Question 29: In which state do you practice?[2]		
Northeast	83	27.7
Midwest	61	20.3
South	113	37.7
West	43	14.3
Other	0	0.0
Prefer not to answer	0	0.0

[1] Number of eligible pharmacists completing the survey (See Table 1).

[2] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

Table 5. Characteristics of Respondents Completing the Survey

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
Question 24: Are you the Pharmacist in Charge for the TIRF REMS Access Program where you work?		
Yes	230	76.7
No	68	22.7
I don't know	2	0.7
Question 25: On average, how many times per month have you dispensed TIRF medicines within the last 6 months		
None	132	44.0
1-2 times per month	81	27.0
3-5 times per month	36	12.0
More than 5 times per month	31	10.3
I don't remember	20	6.7
Question 26: Please select the TIRF medicine(s) that you have dispensed within the last 6 months (select all that apply):[2,3]		
Abstral®	16	9.5
Actiq® or generic Actiq®	127	75.6
Fentora®	85	50.6
Lazanda®	10	6.0
Onsolis®	2	1.2
Subsys®	43	25.6
N/A (answered None to Question 25)	132	

[1] Number of eligible pharmacists completing the survey (See Table 1).

[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

[3] More than one response can be selected, so percentages may not sum to 100%.

N/A = Not applicable.

5.1.3 TIRF Medicines Educational Materials

Pharmacists were asked about their access to educational materials for TIRF medicines, specifically the Full Prescribing Information and the Medication Guide (Table 6). Almost all pharmacists reported they had received or had access to the Full Prescribing Information and the Medication Guide (294, 98.0%; and 292, 97.3%, respectively). Of those with access to these materials, 79.9% and 88.0%, respectively, indicated that they had read the Full Prescribing Information and the Medication Guide.

Table 6. Responses to Questions About TIRF Medicines Educational Materials

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
Question 18: Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you dispense?		
Yes	294	98.0
No	3	1.0
I don't know	3	1.0
Question 19: Did you read the Full Prescribing Information for the TIRF medicine(s) that you dispense?[2]		
Yes	235	79.9
No	49	16.7
I don't know	10	3.4
N/A (answered ***No*** or ***I don't know*** to Question 18)	6	
Question 20: Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you dispense?		
Yes	292	97.3
No	2	0.7
I don't know	6	2.0
Question 21: Did you read the Medication Guide for the TIRF medicine(s) that you dispense?[2]		
Yes	257	88.0
No	29	9.9
I don't know	6	2.1
N/A (answered ***No*** or ***I don't know*** to Question 20)	8	

Table 6. Responses to Questions About TIRF Medicines Educational Materials

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
Question 22: Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?		
Yes[3]	22	7.3
No	265	88.3
I don't know	13	4.3

[1] Number of eligible pharmacists completing the survey (See Table 1).
[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[3] Verbatim text for questions about the information in the Full Prescribing Information or the Medication Guide are presented in Appendix B, Listing 1.
N/A = Not Applicable

5.2 KAB Survey Objectives

5.2.1 Key Risk Message Results

The focus of this section of the document is on the findings for the total eligible respondent population that completed the survey. A summary of results by sub-group is provided in a separate section of the document, Section 5.2.3.

5.2.1.1 Key Risk Message 1

Key Risk Message 1 refers to the pharmacist's knowledge of the specific contraindications for TIRF medicines.

Analysis of responses to components of Question 5 for Key Risk Message 1 showed that a high percentage of pharmacists knew that patients with cancer who are considered opioid-tolerant are those who are taking around-the-clock opioid therapy for cancer pain for one week or longer (281, 93.7%), and are those who are currently taking opioid therapy (261, 87.0%). Somewhat less understood was cancer patients with no known contraindications to the drug fentanyl, but who are not taking around-the-clock opioid therapy, are not considered opioid tolerant (236, 78.7%); however, the correct response rate did increase from the previous survey wave correct response rate of 76.0%.

Analysis of responses to components of Question 7 for Key Risk Message 1 showed that a high percentage of pharmacists knew that TIRF medicines are contraindicated in opioid non-tolerant patients (272, 90.7%) and that death has occurred in opioid non-tolerant patients treated with some fentanyl products (281, 93.7%). Similarly, 237 (79.0%) pharmacists were aware that dose titration for patients starting a TIRF medicine must begin with the lowest available dose for that product, and that TIRF medicines may not be used to treat opioid non-tolerant patients (251, 83.7%), (Table 7). Overall, evidence of understanding of this key risk

information is further supported by the average number of correct responses identified as 6.1 out of a possible 7.

Table 7. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible Completed Pharmacists N=300[1]	
	n	% (95% CI)[3]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:		
5a: Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer		
True[2]	281	93.7 (90.3, 96.1)
False	11	3.7
I don't know	8	2.7
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before		
True	29	9.7
False[2]	261	87.0 (82.7, 90.6)
I don't know	10	3.3
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy		
True	44	14.7
False[2]	236	78.7 (73.6, 83.2)
I don't know	20	6.7

Table 7. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible Completed Pharmacists N=300[1]	
	n	% (95% CI)[3]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True[2]	272	90.7 (86.8, 93.7)
False	19	6.3
I don't know	9	3.0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True[2]	281	93.7 (90.3, 96.1)
False	4	1.3
I don't know	15	5.0
7c: TIRF medicines may be used in opioid non-tolerant patients.		
True	39	13.0
False[2]	251	83.7 (79.0, 87.7)
I don't know	10	3.3
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.		
True[2]	237	79.0 (73.9, 83.5)
False	50	16.7
I don't know	13	4.3

Table 7. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible Completed Pharmacists N=300[1]	
	n	% (95% CI)[3]
Secondary Analysis: Demonstrated Understanding		
0 correct responses	0	0.0
1 correct response	2	0.7
2 correct responses	9	3.0
3 correct responses	5	1.7
4 correct responses	15	5.0
5 correct responses	40	13.3
6 correct responses	79	26.3
7 correct responses	150	50.0
Average number of correct responses	6.1	(5.8, 7.0)[4]

[1] Number of eligible pharmacists completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or component within a question.
[3] All confidence intervals are exact binomial 95% confidence intervals.
[4] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.1.2 Key Risk Message 2

Key Risk Message 2 refers to the pharmacist's knowledge of the approved indications for prescribing TIRF medicines to opioid tolerant patients.

Responses to components of Question 9 *(Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.)* for Key Risk Message 2 indicates that 275 (91.7%) pharmacists were aware that TIRF medicines are indicated for opioid-tolerant patients with breakthrough pain from cancer and not for patients with acute or postoperative pain (86.7%), headache or migraine pain (90.7%), or dental pain (97.0%), (Table 8). For Component 9e *(Chronic non-cancer pain)*, only 43.7% of pharmacists correctly responded that TIRF medicines should not be prescribed for chronic non-cancer pain. Further discussion is provided in Section 5.4.

Overall, evidence of understanding of this key risk information is further supported by the average number of correct responses identified as 4.1 out of a possible 5.

Table 8. Responses Linked to Key Risk Message 2: TIRF Medicines Are Only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (16 Years of Age and Older for Actiq® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible Completed Pharmacists N=300[1]	
	n	% (95% CI)[3]
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.		
9a: Acute or postoperative pain		
Yes	33	11.0
No[2]	260	86.7 (82.3, 90.3)
I don't know	7	2.3
9b: Headache or migraine pain		
Yes	9	3.0
No[2]	272	90.7 (86.8, 93.7)
I don't know	19	6.3
9c: Dental pain		
Yes	5	1.7
No[2]	291	97.0 (94.4, 98.6)
I don't know	4	1.3
9d: Breakthrough pain from cancer		
Yes[2]	275	91.7 (87.9, 94.5)
No	23	7.7
I don't know	2	0.7

Table 8. Responses Linked to Key Risk Message 2: TIRF Medicines Are Only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (16 Years of Age and Older for Actiq® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible Completed Pharmacists N=300[1]	
	n	% (95% CI)[3]
9e: Chronic non-cancer pain		
Yes	146	48.7
No[2]	131	43.7 (38.0, 49.5)
I don't know	23	7.7
Secondary Analysis: Demonstrated Understanding		
0 correct responses	1	0.3
1 correct response	7	2.3
2 correct responses	8	2.7
3 correct responses	41	13.7
4 correct responses	132	44.0
5 correct responses	111	37.0
Average number of correct responses	4.1	(3.9, 5.0) [4]

[1] Number of eligible pharmacists completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or component within a question.
[3] All confidence intervals are exact binomial 95% confidence intervals.
[4] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.1.3 Key Risk Message 3

Key Risk Message 3 refers to the pharmacist's knowledge of the risk factors and signs and symptoms of opioid abuse in patients who take TIRF medicines.

Responses to components of Questions 7, 8, and 10 for Key Risk Message 3 showed that 288 (96.0%) pharmacists were aware that it is important to monitor for signs of abuse and addiction in patients who take TIRF medicines; a personal history of past or current alcohol or drug abuse or family history of drug and alcohol abuse is a risk factor for opioid abuse (298, 99.3%); and TIRF medicines can be abused in a manner similar to other opioid agonists

(283, 94.3%). Somewhat less understood was that a personal history of psychiatric illness is a risk factor for opioid abuse (213, 71.0%), (Table 9). Overall, evidence of understanding of this key risk information is further supported by the average number of correct responses identified as 3.6 out of a possible 4.

Table 9. Responses Linked to Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist and a Schedule II Controlled Substance, With Abuse Liability Similar to Other Opioid Analgesics.

Question	Eligible Completed Pharmacists N=300[1]	
	N	% (95% CI)[3]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True[2]	288	96.0 (93.1, 97.9)
False	7	2.3
I don't know	5	1.7
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.		
8a: A personal history of psychiatric illness		
Yes[2]	213	71.0 (65.5, 76.1)
No	46	15.3
I don't know	41	13.7
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes[2]	298	99.3 (97.6, 99.9)
No	0	0.0
I don't know	2	0.7

Table 9. Responses Linked to Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist and a Schedule II Controlled Substance, With Abuse Liability Similar to Other Opioid Analgesics.

Question	Eligible Completed Pharmacists N=300[1]	
	N	% (95% CI)[3]
Question 10: Please answer True, False, or I don't know for each statement about TIRF medicines.		
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True[2]	283	94.3 (91.1, 96.7)
False	12	4.0
I don't know	5	1.7
Secondary Analysis: Demonstrated Understanding		
0 correct responses	1	0.3
1 correct response	1	0.3
2 correct responses	12	4.0
3 correct responses	87	29.0
4 correct responses	199	66.3
Average number of correct responses	3.6	(3.4, 4.0) [4]

[1] Number of eligible pharmacists completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or component within a question.
[3] All confidence intervals are exact binomial 95% confidence intervals.
[4] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.1.4 Key Risk Message 4

Key Risk Message 4 refers to the pharmacist's knowledge that TIRF medicines are not interchangeable regardless of the route of administration.

Responses to components of Question 10 (b, c, and d) for Key Risk Message 4 showed that 280 pharmacists (93.3%) understood TIRF medicines are not interchangeable with each other regardless of the route of administration; 279 pharmacists (93.0%) understood the conversion of one TIRF medicine to another may result in a fatal overdose; and 270 pharmacists (90.0%) understood dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (Table 10). Overall, evidence of understanding of this key risk information is further supported by the average number of correct responses identified as 2.8 out of a possible 3.

Table 10. Responses Linked to Key Risk Message 4: TIRF Medicines Are Not Interchangeable with Each Other, Regardless of Route of Administration.

Question	Eligible Completed Pharmacists N=300[1]	
	n	% (95% CI)[3]
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
10b: TIRF medicines are interchangeable with each other regardless of route of administration.		
True	13	4.3
False[2]	280	93.3 (89.9, 95.9)
I don't know	7	2.3
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.		
True[2]	279	93.0 (89.5, 95.6)
False	13	4.3
I don't know	8	2.7
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True[2]	270	90.0 (86.0, 93.2)
False	20	6.7
I don't know	10	3.3
Secondary Analysis: Demonstrated Understanding		
0 correct responses	3	1.0
1 correct response	9	3.0
2 correct responses	44	14.7
3 correct responses	244	81.3
Average number of correct responses	2.8	(2.6, 3.0)[4]

[1] Number of eligible pharmacists completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or component within a question.
[3] All confidence intervals are exact binomial 95% confidence intervals.
[4] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.2 Other Survey Questions

5.2.2.1 Additional Questions about TIRF Medicines Safety

Table 11 summarizes the pharmacists' responses to additional questions about the safe use of TIRF medicines beyond those associated with the key risk messages. Responses to these additional questions generally confirmed the pharmacists' understanding of the safety issues and the risks associated with taking TIRF medicines.

Question 6 (see Table 11) assists in determining the pharmacist understanding of around-the-clock usage, and 63.3% of pharmacists correctly indicated that a cancer patient should not be started on a TIRF medicine and an around-the-clock opioid at the same time, and 74.0% understood a cancer patient who had been on an around-the-clock opioid for one day should not start taking a TIRF medicine for breakthrough pain. For Question 11, greater than 70% of pharmacists correctly identified an opioid drug/dose regimen that, when taken by the patient, identifies patients as opioid tolerant according to the labeling for TIRF medicines. However, fewer understood that an equianalgesic dose of another oral opioid could also meet the definition of opioid tolerant (correct response 59.0%; Table 11). For Question 13, pharmacists correctly indicated that TIRF medicines may not be sold, loaned, or transferred to another pharmacy (92.0%); pharmacy staff who dispense TIRF medicines must be educated on the requirements of the TIRF REMS Access Program (94.7%); and that TIRF medicines with the same route of administration cannot be substituted with each other (97.7%).

Thirteen (86.7%) inpatient pharmacists correctly indicated that it is not OK to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for home use (Table 12).

Table 11. Responses to Additional Questions about the Safe Use of TIRF Medicines

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
6a: A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time.		
True	85	28.3
False[2]	190	63.3
I don't know	25	8.3

Table 11. Responses to Additional Questions about the Safe Use of TIRF Medicines

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
6b: A cancer patient who has been on an around-the-clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.		
True	57	19.0
False[2]	222	74.0
I don't know	21	7.0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.		
8c: A family history of asthma		
Yes	25	8.3
No[2]	260	86.7
I don't know	15	5.0
Question 11: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:		
11a: 8 mg oral hydromorphone/day		
True[2]	229	76.3
False	31	10.3
I don't know	40	13.3
11b: 60 mg oral morphine/day		
True[2]	254	84.7
False	15	5.0
I don't know	31	10.3
11c: 30 mg oral oxycodone/day		
True[2]	220	73.3
False	38	12.7
I don't know	42	14.0

Table 11. Responses to Additional Questions about the Safe Use of TIRF Medicines

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
11d: 25 mcg transdermal fentanyl/hour		
True[2]	223	74.3
False	31	10.3
I don't know	46	15.3
11e: 25 mg oral oxymorphone/day		
True[2]	213	71.0
False	26	8.7
I don't know	61	20.3
11f: An equianalgesic dose of another oral opioid		
True[2]	177	59.0
False	57	19.0
I don't know	66	22.0
Question 13: Please answer True, False, or I don't know for each statement about TIRF medicines.		
13a: TIRF medicines may be sold, loaned, or transferred to another pharmacy.		
True	11	3.7
False[2]	276	92.0
I don't know	13	4.3
13b: All pharmacy staff that dispenses TIRF medicines must be educated on the requirements of the TIRF REMS Access Program.		
True[2]	284	94.7
False	10	3.3
I don't know	6	2.0

Table 11. Responses to Additional Questions about the Safe Use of TIRF Medicines

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
13c: TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.		
True	2	0.7
False[2]	293	97.7
I don't know	5	1.7

[1] Number of eligible pharmacists completing the survey (See Table 1).

[2]Indicates the correct response(s) to each question or component within a question.

Table 12. Responses to Additional Questions about the Safe Use of TIRF Medicines: Question asked of Inpatient Pharmacists, Only

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
Question 17: Please answer True, False, or I don't know for the following statement about TIRF medicines. (Inpatient pharmacists, only)		
It is OK to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for use at home.[3]		
True	2	13.3
False[2]	13	86.7
I don't know	0	0.0

[1] Question asked of inpatient pharmacists only.

[2] Indicates the correct response(s) to each question or component within a question.

[3] This question is presented only to a sub-group of pharmacists. Percentages are based on the number of pharmacists to whom this question was presented.

5.2.2.2 Pharmacist Activities When Dispensing TIRF Medicines

Pharmacists were asked about specific activities performed when dispensing TIRF medicines (Table 13).

Of the 300 eligible pharmacists, 174 (58.0%) responded they always ask their patients (or a patient's caregiver) about the presence of children in the home; 22.7% responded that they ask only with the first prescription. Additionally, 74.7% responded they always instruct

patients (or their caregivers) not to share TIRF medicines, 72.0% responded they always counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal, 74.7% responded they always instruct patients (or their caregivers) to keep TIRF medicines out of reach of children, 67.7% responded they always instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines, and 89.3% responded they always give patients (or their caregivers) the Medication Guide for TIRF medicine.

Table 13. Responses to Questions about Activities When Dispensing TIRF Medicines

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
Question 12: How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.		
12a: Ask patients (or their caregivers) about the presence of children in the home.		
Always	174	58.0
Only with the first prescription	68	22.7
Sometimes	33	11.0
Never	14	4.7
I don't know	11	3.7
12b: Instruct patients (or their caregivers) not to share TIRF medicines with anyone else.		
Always	224	74.7
Only with the first prescription	45	15.0
Sometimes	17	5.7
Never	6	2.0
I don't know	8	2.7
12c: Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal.		
Always	216	72.0
Only with the first prescription	53	17.7
Sometimes	16	5.3
Never	6	2.0
I don't know	9	3.0

Table 13. Responses to Questions about Activities When Dispensing TIRF Medicines

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
12d: Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure.		
Always	224	74.7
Only with the first prescription	48	16.0
Sometimes	17	5.7
Never	3	1.0
I don't know	8	2.7
12e: Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines.		
Always	203	67.7
Only with the first prescription	63	21.0
Sometimes	23	7.7
Never	3	1.0
I don't know	8	2.7
12f: Give patients (or their caregivers) the Medication Guide for their TIRF medicine.		
Always	268	89.3
Only with the first prescription	20	6.7
Sometimes	3	1.0
Never	1	0.3
I don't know	8	2.7

[1] Number of eligible pharmacists completing the survey (See Table 1).

Specific pharmacy types (inpatient, outpatient, and CSP pharmacies) were each asked a single different question regarding pharmacy systems and processes. Question 14 was presented only to pharmacy respondents from inpatient pharmacies (N=15) as identified through the access code entered by the respondent (Table 14). Of the 15 respondents, 7 (46.7%) reported their pharmacy has processes to ensure compliance with the TIRF REMS Access Program requirements.

Table 14. Responses to All Questions about Activities When Dispensing TIRF Medicines: Asked of Inpatient Pharmacies Only

Question	Eligible Completed Inpatient Pharmacists N=15[1]	
	n	%
Question 14: Does the inpatient pharmacy where you work have an established system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access Program? [Inpatient pharmacists only][2]		
Yes	7	46.7
No	5	33.3
I don't know	3	20.0

[1] Number of eligible inpatient pharmacists completing the survey.
[2] This question is presented only to a sub-group of pharmacists. Percentages are based on the number of inpatient pharmacists to whom this question was presented.

Question 15 was presented only to pharmacy respondents from outpatient pharmacies (n=284) as identified through the access code entered by the respondent. This sub-population did not include respondents from CSPs (Table 15). Of the 284 respondents, 254 (89.4%) reported their pharmacy processes prescriptions for TIRF medicines through their pharmacy management system.

Table 15. Responses to All Questions about Activities When Dispensing TIRF Medicines: Outpatient Pharmacists Only

Question	Eligible Completed Outpatient Pharmacists N=284[1]	
	n	%
Question 15: Does the outpatient or retail pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the pharmacy management system? [Outpatient pharmacists only][2]		
Yes	254	89.4
No	6	2.1
I don't know	24	8.5

[1] Number of eligible outpatient pharmacists completing the survey.
[2] This question is presented only to a sub-group of pharmacists. Percentages are based on the number of outpatient pharmacists to whom this question was presented.

Question 16 was presented only to pharmacy respondents from CSPs (N=1) as identified through the access code entered by the respondent (Table 16). The single respondent indicated his/her pharmacy processes all prescriptions for TIRF medicines through the TIRF REMS Access Call Center.

Table 16. Responses to All Questions about Activities When Dispensing TIRF Medicines: Closed System Pharmacy Outpatient Pharmacists Only

Question	Eligible Completed CSP Pharmacists N=1[1]	
	n	%
Question 16: Does the pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the TIRF REMS Access Call Center? [CSP Outpatient pharmacists only][2]		
Yes	1	100.0
No	0	0.0
I don't know	0	0.0

[1] Number of eligible CSP outpatient pharmacists completing the survey.
[2] This question is presented only to a sub-group of pharmacists. Percentages are based on the number of CSP pharmacists to whom this question was presented.

5.2.3 Sub-group Analysis of Responses to Key Risk Messages

To further assess pharmacist understanding of key risk messages, sub-group analyses as described in Section 4.1.2 were conducted. Sub-group analysis of time to complete the survey for telephone respondents was not done since there were less than 20 respondents in this sub-group (telephone respondents; n=13). For the remaining sub-group analyses that were performed, results are similar to the results in the primary analysis population, and no trends are evident, with the exception of a lower correct response rate for those who took the survey by telephone for most questions in Key Risk Message 1 and for Key Risk Message 4, Question 10 d. The full set of sub-group analysis tables is provided in Appendix B.

5.3 Spontaneous Reporting of Adverse Events, Product Complaints, or Medical Information Requests

Among all survey respondents (N=300, Table 1), there were no adverse events or product complaints reported. In the Internet survey, respondents had the option to write in any questions they had when asked "*What are your questions*?" Respondents who took the telephone survey could have spontaneously asked a question. This resulted in 19 individual responses by various completers, of which 8 were requests for medical information and 11 were indications that the free text field was not applicable or they had no questions (Appendix B, Listing 1).

5.4 Summary of Correct Responses for Key Risk Messages

The four key risk messages included 19 components detailing these key risk messages. A tabulated summary of correct response rates for each component is presented below (Table 17). The correct response rate was greater than or equal to 90% for 11 of the key risk message components, between 70% and 90% for 7 components, and was 43.7% for a single component (Question 9*: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients?* Component 9E*: Chronic non-cancer pain;* Correct response *"No"*) which is below the desired level of understanding of 65%.

Table 17. Summary of Correct Responses for Key Risk Messages

Key Risk Message	Question #	Question	Correct Responses	
			N	% (95% CI)
Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients	5. **Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:**			
	5a	Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer (*Correct Response "True"*)	281	93.7 (90.3, 96.1)
	5b	Who are not currently taking opioid therapy, but have taken opioid therapy before (*Correct Response "False"*)	261	87.0 (82.7, 90.6)
	5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy (*Correct Response "False"*)	236	78.7 (73.6, 83.2)
	7. **Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.**			
	7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose (*Correct Response "True"*)	272	90.7 (86.8, 93.7)
	7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products (*Correct Response "True"*)	281	93.7 (90.3, 96.1)
	7c	TIRF medicines may be used to treat opioid non-tolerant patients (*Correct Response "False"*)	251	83.7 (79.0, 87.7)

Table 17. Summary of Correct Responses for Key Risk Messages

Key Risk Message	Question #	Question	Correct Responses	
			N	% (95% CI)
Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients (continued)	7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine (*Correct Response "True"*)	237	79.0 (73.9, 83.5)
Key Risk Message 2: TIRF Medicines are only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (16 Years of Age and Older for Actiq® Brand and Generic Equivalents) who are already Receiving and who are Tolerant to Around-the-Clock Opioid Therapy for their Underlying Persistent Cancer Pain	9. **Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option**.			
	9a	Acute or postoperative pain (*Correct Response "No"*)	260	86.7 (82.3, 90.3)
	9b	Headache or migraine pain (*Correct Response "No"*)	272	90.7 (86.8, 93.7)
	9c	Dental pain (*Correct Response "No"*)	291	97.0 (94.4, 98.6)
	9d	Breakthrough pain from cancer (*Correct Response 'Yes'*)	275	91.7 (87.9, 94.5)
	9e	Chronic non-cancer pain (*Correct Response "No"*)	131	43.7 (38.0, 49.5)

Table 17. Summary of Correct Responses for Key Risk Messages

Key Risk Message	Question #	Question	Correct Responses	
			N	% (95% CI)
Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist and a Schedule II Controlled Substance, with Abuse Liability Similar to other Opioid Analgesics	7. **Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.**			
	7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines *(Correct Response True)*	288	96.0 (93.1, 97.9)
	8. **Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option**.			
	8a	A personal history of psychiatric illness (*Correct Response "Yes"*)	213	71.0 (65.5, 76.1)
	8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse (*Correct Response "Yes"*)	298	99.3 (97.6, 99.9)
	10. **Please answer True, False, or I don't know for each statement about TIRF medicines**.			
	10a	TIRF medicines can be abused in a manner similar to other opioid agonists (*Correct Response "True"*)	283	94.3 (91.1, 96.7)

Table 17. Summary of Correct Responses for Key Risk Messages

Key Risk Message	Question #	Question	Correct Responses	
			N	% (95% CI)
Key Risk Message 4: TIRF Medicines are not Interchangeable with each other, Regardless of Route of Administration	10b	TIRF medicines are interchangeable with each other regardless of route of administration (*Correct Response "False"*)	280	93.3 (89.9, 95.9)
	10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption (*Correct Response "True"*)	279	93.0 (89.5, 95.6)
	10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (*Correct Response "True"*)	270	90.0 (86.0, 93.2)

6. FDA FEEDBACK

FDA provided the following feedback on the 24-month assessment of the TIRF REMS, received in August 2014. This feedback was received too late to incorporate changes into the 36-month Pharmacist KAB survey but changes based on FDA feedback will be incorporated into the 48-month Pharmacist KAB survey.

- In the pharmacist survey, 81% of those surveyed functioned as the pharmacist in charge for their operations. In future pharmacist surveys, consider ensuring that a higher percentage of non-supervisory dispensing pharmacists are included.

- Given that pharmacists often have the opportunity to see all of the prescriptions that a patient is taking, include a question in the pharmacist survey regarding the CYP3A4 interactions with TIRFs.

- Also include a question in the pharmacist survey regarding their understanding that patients are to stop taking their TIRF when they stop taking their around-the-clock opioid.

7. DISCUSSION AND CONCLUSIONS

Discussion

For the pharmacist KAB survey invitations (and reminders) were sent to a random sample of pharmacies enrolled in the TIRF REMS Access Program. From among those who responded to the invitation, 300 pharmacists completed the survey; thus the program sample size was achieved within the specific time period.

The specific goals of the TIRF medicines pharmacist KAB survey were to assess pharmacist understanding of the risks associated with TIRF medicine use, the specific indications for treatment with TIRF medicines, and that TIRF medicines are contraindicated in opioid non-tolerant patients. They survey also included questions about the pharmacists' access to educational materials for TIRF medicines.

In this 36-month survey, all but one of the questions/components included as part of the key risk messages had a correct response rate of >70%. There was only one question within a key risk message (Question 9 [*Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients?*] in Key Risk Message 2) that had a component with an understanding rate below the desired threshold of 65% (Component 9e: *Chronic non-cancer pain*; correct response "*No*"; correct response rate 43.7%). For the other 4 components of Question 9, the desired responses were greater than 86% in the 36-month survey. It should be noted that pharmacist knowledge of uses for which TIRF medicines are not indicated is not a goal of the TIRF REMS. This concept also scored low patients/caregivers (25.3%; presented as *Long-lasting painful conditions not caused by cancer*).

In addition, there were two questions included as part of the additional questions about the safe use of TIRF medicines (and not included as part of a key risk message) that had a component with an understanding rate below 65% (See Table 18). The correct response for Component 6a which addresses knowledge that a cancer patient should not be started on a TIRF medicine and an around-the-clock opioid at the same time was 63.3%. This concept also scored low for prescribers (60.0%) during this reporting period. The correct response for component 11f that addresses the knowledge that patients are considered opioid-tolerant if taking an equianalgesic dose of another oral opioid one week or longer, was 59.0%. This concept also scored low for prescribers (59.0%) during this reporting period.

As also shown in Table 18, the correct response rate was consistently low for Components 6a and 11f between the 24-month and 36-month Pharmacist KAB surveys and for Component 9e across all three surveys (the 12-month, the 24-month and the 36-month Pharmacist KAB surveys).

Table 18. Correct/Desired Response Rate of Low Scoring Questions Across the Three Pharmacist KAB Survey Waves.

36-Month Survey Question Number	Questions as Presented in the 36-Month Survey	12-Month Survey Correct/Desired Response Rate (%)	24-Month Survey Correct/Desired Response Rate (%)	36-Month Survey Correct/Desired Response Rate (%)
6[2]	**Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.**			
6a[2]	A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time. ***(Desired Response False)***	Not asked	65.3	63.3
9[1]	**Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option**			

Table 18. Correct/Desired Response Rate of Low Scoring Questions Across the Three Pharmacist KAB Survey Waves.

36-Month Survey Question Number	Questions as Presented in the 36-Month Survey	12-Month Survey Correct/Desired Response Rate (%)	24-Month Survey Correct/Desired Response Rate (%)	36-Month Survey Correct/Desired Response Rate (%)
9e[1]	Chronic non-cancer pain ***(Desired Response No)***	29.8[2]	47.0	43.7
11[2]	**Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:**			
11f[2]	An equianalgesic dose of another oral opioid ***(Desired Response True)***	Not asked	59.0	59.0

[1] This was part of Question 8 (8e) in 12-month Pharmacist KAB survey. Question 8 was worded as follows for the 12-month KAB survey: For which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.
[2] Not asked as a key risk message.

Although responses for components in Table 18 are below the desired threshold of 65%, the responses for other components within the same questions or for similar concepts are high. Although the majority of the respondents scored less than the desired threshold of 65% in Component 6a, 74.0% of the respondents understood a cancer patient who had been on an around-the-clock opioid for one day should not start taking a TIRF medicine for breakthrough pain (Component 6b). In addition, the majority of the respondents (93.7%) indicated patients with cancer who are considered opioid tolerant are those who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer (Component 5a, Key Risk Message 1). For Question 11, which also addresses opioid tolerance by asking the respondent to identify specific medications and doses that if taken by a patient for one week or longer would identify the patient as opioid tolerant, most of the respondents (>71%) identified a response for all components, except component 11f (*equianalgesic dose of another oral opioid)* having a lower response rate (59.0%).

Conclusions

The consistently high level of pharmacist understanding of key risk messages in the 24-month and 36-month surveys indicates that the Education Program for Prescribers and Pharmacists is meeting the goals of the TIRF REMS. The TRIG will evaluate the concepts that have scored low among stakeholders to determine if any action is warranted. As stated above, changes will be implemented into the 48-month Pharmacist KAB survey based on FDA feedback received on the 24-month assessment report. The TRIG will continue to work with the FDA to refine, on a continual basis, the steps to mitigate risks associated with TIRF medicines.

Appendix A Pharmacy Survey Protocol

PROTOCOL TITLE:	**Quantitative Testing of Pharmacist Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)** **Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)** **Depomed, Inc.** **Galena Biopharma, Inc.** **Insys Therapeutics** **Mallinckrodt Pharmaceuticals** **Meda Pharmaceuticals** **Mylan, Inc.** **Par Pharmaceutical, Inc.**
VERSION:	**6.0**
DATE:	**18MAY2014**
APPROVED:	**Final**

TABLE OF CONTENTS PAGE

	TABLE OF CONTENTS	2
1.	LIST OF ABBREVIATIONS	3
2.	BACKGROUND	4
3.	OBJECTIVES OF THE EVALUATION SURVEY	5
4.	METHODS	5
4.1	Survey Design	5
4.1.1	Qualitative Research on the Survey	6
4.1.2	Questions and Statements on REMS Goals	6
4.1.3	Additional Questions	9
4.2	Participant Recruitment	10
4.2.1	Measures to Minimize Bias in the Sample	10
5.	STUDY POPULATION	10
5.1.1	Sample Size	10
5.1.2	Inclusion Criteria	11
5.1.3	Exclusion Criteria	11
6.	SURVEY PROCESS	12
6.1	Screening and Survey Administration	12
6.1.1	Telephone	12
6.1.2	Internet	12
6.2	Measures to Minimize Bias in the Survey Process	12
7.	ANALYSIS	13
7.1.1	Analysis Population	13
7.1.1.1	Description of Primary Analyses	13
7.1.1.2	Description of Secondary Analyses	14
8.	SAFETY EVENT REPORTING	14
9.	PRIVACY PROTECTION AND CONFIDENTIALITY	14

LIST OF APPENDICES

Appendix A	Pharmacist Questionnaire	15
Appendix B	SAMPLE Pharmacist Invitation Letter	33

1. LIST OF ABBREVIATIONS

CATI	Computer-Assisted Telephone Interviewing
CSP	Closed System Pharmacy
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ISI	Important Safety Information
KAB	Knowledge, Attitudes and Behavior
PI	Prescribing Information
REMS	Risk Evaluation and Mitigation Strategy
SE PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access Program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Meda Pharmaceuticals; Mallinckrodt Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients

2. Preventing inappropriate conversion between TIRF medicines

3. Preventing accidental exposure to children and others for whom it was not prescribed

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

An important component of the TIRF REMS is the conduct of quantitative evaluation surveys to assess pharmacists' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS educational materials, enrollment form, and Prescribing Information (PI). This protocol will describe the administration of the surveys that will be conducted among pharmacists who are enrolled in the TIRF REMS Access Program.

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

3. OBJECTIVES OF THE EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of pharmacists around the following key information and risk messages communicated through REMS:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.

2. TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 or older for Actiq® and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

3. TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.

4. TIRF medicines are not interchangeable with each other, regardless of route of administration.

5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey will also collect data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC), and will be administered by UBC.

4.1 Survey Design

This survey will be conducted among a sample of pharmacists who are enrolled in the TIRF REMS Access Program. Respondents who have participated in a previous wave of the TIRF survey will not be eligible to participate in subsequent survey waves.

The survey will be administered using the following modalities:

- Self-administered via the Internet through a secure website

- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take up to 20 minutes.

The survey included in Appendix A is written to reflect wording for both methods of survey administration: Internet-based and telephone.

All respondents who complete the survey and who provide their contact information will be mailed a $50 honorarium for their time.

4.1.1 Qualitative Research on the Survey

The FDA provided feedback to the TRIG on the Knowledge, Attitude, and Behavior (KAB) survey results for pharmacists included in the 12-month REMS Assessment results. The FDA requested that the TRIG investigate the causes for low correct response rates to specific questions in the survey by conducting research to determine the reasons for the poor performance on these questions and to assess proposed revised wording to select questions. Qualitative research was performed in 2013 prior to Wave 2 of the survey. Findings were incorporated into the survey and results from the revised survey were included in the 24-month REMS Assessment Report,

4.1.2 Questions and Statements on REMS Goals

The KAB questionnaire is made up of multiple-choice, close-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and one open-ended question. These will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3.

Questions will be presented in several formats:

- Statements or questions asking the respondent to indicate whether a statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use “yes” or “no” as potential response options);

- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and

- One question allowing for the respondent to list questions or comments.

Questionnaires will be analyzed to determine pharmacist understanding of each key risk message.

For statements or questions that use “true” or “yes” vs. “false” or “no” response options, the desired response for the key risk messages is generally “true” or “yes” indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions are

formatted to have the respondent disagree with the statement as written by providing response options of “false” or “no” to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired response**
5	Please select True, False, or I don’t know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a	Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	**TRUE**
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before	**FALSE**
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	**FALSE**
7	Please answer True, False, or I don’t know for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**TRUE**
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	**TRUE**
7c	TIRF medicines may be used in opioid non-tolerant patients.	**FALSE**
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	**TRUE**

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.		
Question No.	**Question**	**Desired response**
9	Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a	Acute or postoperative pain	**NO**
9b	Headache or migraine pain	**NO**
9c	Dental pain	**NO**
9d	Breakthrough pain from cancer	**YES**
9e	Chronic non-cancer pain	**NO**

Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance with abuse liability similar to other opioid analgesics.		
Question No.	**Question**	**Desired response**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**TRUE**
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a	A personal history of psychiatric illness	**YES**
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**YES**
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10a	TIRF medicines can be abused in a manner similar to other opioid agonists.	**TRUE**

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired response**
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10b	TIRF medicines are interchangeable with each other regardless of route of administration.	**FALSE**
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	**TRUE**
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**TRUE**

4.1.3 Additional Questions

The survey includes questions about the requirements of the TIRF REMS Access Program, receipt and understanding of the TIRF educational materials, and behaviors. The following question about behaviors will be asked after the key risk message questions.

Question 12: How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.
Ask patients (or their caregivers) about the presence of children in the home
Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
Give patients (or their caregivers) the Medication Guide for their TIRF medicine

Demographic information will be collected at the end of the survey.

4.2 Participant Recruitment

A random sample of "pharmacists in charge" from pharmacies that are enrolled in the TIRF REMS Access Program will be invited to participate via an invitation letter. Any pharmacist who works at an enrolled pharmacy may participate. The text of the sample written invitation to pharmacists can be found in Appendix B.

If the required number of completed surveys is not achieved within the expected timeframe of approximately one to two weeks after the first mailing, reminder letters will be sent to non-responders from the original sample with subsequent fax, e-mail, or United States (US) Mail follow-up to maximize participation. The distribution within the mailing to the second sample will be adjusted in accordance with the allocation in the original sample. If these efforts do not result in the required number of surveys within two to three weeks, then a new sample of pharmacists will be randomly selected. The unique code provided in the invitation letter will be linked to the type of pharmacy (inpatient, outpatient, or Closed System Pharmacy [CSP]) in which the pharmacist works, based on the information provided as part of the TIRF REMS Access Program enrollment.

All respondents who complete the survey and who provide their contact information will be mailed a $50 honorarium to thank them for their participation. The mailing will include a Thank You Letter, a copy of the Important Safety Information (ISI), and a copy of the correct answers to key risk message questions.

4.2.1 Measures to Minimize Bias in the Sample

The sample of participating pharmacists will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of pharmacies (e.g., chain and independent store) for participation.

Pharmacists will be offered Internet-based or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the Internet-based survey or when calling the Survey Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

5. STUDY POPULATION

5.1.1 Sample Size

A sample of 300 pharmacists who are enrolled in the TIRF REMS Access Program is proposed for each survey wave. The size of the sample was determined based on both practical and statistical considerations. There is no target comprehension rate specified *a priori*. A sample of 300 completed surveys will allow estimation of the comprehension rate

for each risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval	
5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.2 Inclusion Criteria

Pharmacists who work at pharmacies that are enrolled in the TIRF REMS Access Program are eligible to participate in this survey, with the exceptions noted below.

5.1.3 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Pharmacists who have previously participated in the TIRF REMS KAB survey.
- Pharmacists or their immediate family members who have ever worked for Anesta LLC; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc.; Par Pharmaceutical, Inc.; Teva Pharmaceuticals, Ltd.; UBC; McKesson Specialty Care Solutions; RelayHealth; or the FDA.

6. SURVEY PROCESS

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm pharmacist eligibility. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, the respondent is immediately notified with a "thank you" message that survey participation has ended. If eligible, the respondent is allowed to continue survey participation.

The data entry system used for both methods of survey administration has been validated and is secure for receiving and storing survey data. An Internet-based data repository will be used to store survey data and other relevant program information. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Pharmacist-identifying information will be stored separately from survey data.

6.1.1 Telephone

A trained interviewer from the Survey Coordinating Center will conduct the telephone interviews using a CATI program. The screening and main elements of the questionnaire will be administered sequentially during the same telephone call.

Telephone interviewing allows participation of pharmacists who do not have Internet access or prefer taking the survey over the telephone. It will also be convenient for pharmacists to participate since they can call in and be interviewed at their convenience during the specified time period when the Survey Coordinating Center is available.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If the pharmacist selects to participate in the survey via the Internet, he/she will be directed to a secured website where he/she will be instructed to complete screening questions. An Internet-based survey will be convenient for respondents to participate since they can complete the questionnaire at any convenient time and location during the specified time period when the Survey Coordinating Center is available.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer the survey.

All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question

once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. The data from the sample population will be reported using frequency distributions of responses to all questions.

The following will be reported as part of this analysis:

- The number of invitations issued to pharmacists
- The number of reminder letters issued to pharmacists
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents eligible for participation who answered all questions presented to them
- Representativeness of pharmacists based on geography
- Description of survey participants, including:
    - Gender
    - Years of professional experience
    - How many times per month TIRF medicines dispensed in the last 6 months

Additional descriptive statistics may be reported as appropriate.

7.1.1 Analysis Population

The analysis population will be based on eligible pharmacists who completed all questions presented to them in the survey ("completers").

7.1.1.1 Description of Primary Analyses

Primary analyses are done for all key risk messages using data from all completers. The primary analysis for a key risk message evaluates the rate for each correct response to each individual question/item defined by the key risk message. The specific correct response to each question/item is identified in the body of the risk message table.

7.1.1.2 Description of Secondary Analyses

Secondary analyses are done only for those key risk messages that contain multiple questions/items using data from all completers. The secondary analysis entails a frequency distribution of the number of completers who got 0, 1, etc. correct responses across the total number of items for the given key risk message.

8. SAFETY EVENT REPORTING

The term 'Safety Event' is defined as any information reported by a survey respondent that meets the criteria of an adverse event or product complaint. While it is not the intention of the survey to solicit the report of information that meets the criteria of a Safety Event, it is possible that a respondent may spontaneously report information that meets this criteria in free text fields of the survey (Internet-based administration) or while in conversation with the Survey Coordinating Center (telephone-based administration). The Internet-based questionnaires will be monitored for any comments recorded in the free text fields. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. Respondents will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact them if they have questions about the survey. Information on all reports (Internet or telephone) that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE PSP.

9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The electronic data capture (EDC) system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail the $50 honorarium, a Thank You Letter, correct survey responses to key risk message questions, and the ISI after the survey is completed. Respondent contact information is also needed in the event that a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information (see Section 8 above).

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to dispense TIRF medicines.

Appendix A Pharmacist Questionnaire

Survey Legend

- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.

- **(INTERVIEWER)** is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by telephone only (for example, spontaneous adverse event reporting).

- **[ONLINE]** indicates a question is worded specifically for administering the survey online. **[PHONE]** indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.

- **[BEGIN ONLINE/PHONE SURVEY CONTENT]** and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.

- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

  Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.

- **[RANDOMIZE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as "I don't know," "Prefer not to answer" or "None of the above" will always appear at the end of the randomized responses.

- **[GO TO Qx]** (skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

- **[FREE TEXT]** indicates to the programmer that one line should be provided for data entry.

- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be

provided for data entry (for example, two address lines).

- **[DROP-DOWN LIST INPUT WITH STATES TABLE]** indicates to the programmer that the response should be a drop-down list containing the states in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

Northeast Region

- New England Division - ME, NH, VT, MA, RI, CT
- Middle Atlantic Division - NY, NJ, PA

Midwest Region

- East North Central Division - OH, IN, IL, MI, WI
- West North Central Division - MN, IA, MO, ND, SD, NE, KS

South Region

- South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
- East South Central Division - KY, TN, AL, MS
  West South Central Division - AR, LA, OK, TX

West

Survey Legend

- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV
- Pacific Division WA, OR, CA, AK, HI

The following US territories are categorized as Other: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

[BEGIN SURVEY CONTENT]

[ONLINE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess pharmacists' understanding of the safe use and dispensing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc. The survey will take 15-20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to dispense TIRF medicines.

How We Use Your Information

Your answers to the survey questions will be combined with answers given by other pharmacists taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 honorarium for your time and participation.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

How to Learn More about This Survey

If you have questions about the survey, or problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Be sure to write down this telephone number; it will not be displayed again.

Taking the Survey

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

[PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess pharmacists' understanding of the safe use and dispensing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." **(INTERVIEWER: Say "TIRF" then spell out T-I-R-F)** The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc. The survey will take 15-20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to dispense TIRF medicines.

Now I would like to read some information about how your contact information will be used.

Your answers to the survey questions will be combined with answers given by other pharmacists taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 honorarium for your time and participation.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

Now I would like to tell you some information about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

Now I will tell you how you can learn more about this survey. Please have a pen or pencil ready to write down a telephone number you can call should you have any questions about the survey. If you have questions about the survey, please ask me at any time. If you have questions at a later time, please contact the Survey Coordinating Center at 1-877-379-3297.

Please feel free to ask me to repeat any questions or statements as we go through the survey. Once you have answered a question and moved on, you cannot go back and change your answers. Thank you for your participation in this survey.

[END PHONE PREAMBLE 1]

[BEGIN INCLUSION/EXCLUSION QUESTIONS]

1. Your agreement to participate in this survey confirms mutual understanding in connection with completion of the survey and the fair market value of the payment to be rendered in connection with those services.

   Do you agree to participate in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

   - ○ Yes **[TERMINATE]**
   - ○ No
   - ○ I don't know **[TERMINATE]**

3. Do you work in a pharmacy that is enrolled in the TIRF REMS Access Program?

   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

4. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

   - □ Anesta LLC **[TERMINATE]**
   - □ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**
   - □ Depomed, Inc. **[TERMINATE]**
   - □ Galena Biopharma, Inc. **[TERMINATE]**
   - □ Insys Therapeutics **[TERMINATE]**

- □ Mallinckrodt Pharmaceuticals **[TERMINATE]**
- □ McKesson Specialty Care Solutions **[TERMINATE]**
- □ Meda Pharmaceuticals **[TERMINATE]**
- □ Mylan, Inc. **[TERMINATE]**
- □ Par Pharmaceutical, Inc. **[TERMINATE]**
- □ RelayHealth **[TERMINATE]**
- □ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- □ United BioSource Corporation **[TERMINATE]**
- □ FDA **[TERMINATE]**
- □ None of these apply **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- □ I don't know **[TERMINATE]**
- □ Prefer not to answer **[TERMINATE]**

[END INCLUSION/EXCLUSION QUESTIONS]

5. Please select True, False, or I don't know for each of the following.

According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
5a.	Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	○	○	○
5b.	Who are not currently taking opioid therapy, but have taken opioid therapy before	○	○	○
5c.	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	○	○	○

6. Please answer True, False, or I don't know for each statement based on the labeling for

TIRF medicines.

[RANDOMIZE LIST]	True	False	I don't know
6a. A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time.	○	○	○
6b. A cancer patient who has been on an around-the-clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.	○	○	○

7. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

[RANDOMIZE LIST]	True	False	I don't know
7a. TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	○	○	○
7b. Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	○	○	○
7c. TIRF medicines may be used in opioid non-tolerant patients.	○	○	○
7d. Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	○	○	○
7e. It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	○	○	○

8. Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
8a.	A personal history of psychiatric illness	○	○	○
8b.	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	○	○	○
8c.	A family history of asthma	○	○	○

9. Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
9a.	Acute or postoperative pain	○	○	○
9b.	Headache or migraine pain	○	○	○
9c.	Dental pain	○	○	○
9d.	Breakthrough pain from cancer	○	○	○
9e.	Chronic non-cancer pain	○	○	○

10. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
10a.	TIRF medicines can be abused in a manner similar to other opioid agonists.	○	○	○
10b.	TIRF medicines are interchangeable with each other regardless of route of administration.	○	○	○
10c.	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	○	○	○
10d.	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	○	○	○

11. Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:

	[RANDOMIZE LIST]	True	False	I don't know
11a.	8 mg oral hydromorphone/day	○	○	○
11b.	60 mg oral morphine/day	○	○	○
11c.	30 mg oral oxycodone/day	○	○	○
11d.	25 mcg transdermal fentanyl/hour	○	○	○
11e.	25 mg oral oxymorphone/day	○	○	○
11f.	An equianalgesic dose of another oral opioid	○	○	○

12. How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.

	[RANDOMIZE LIST]	Always	Only with the first prescription	Sometimes	Never	I don't know
12a	Ask patients (or their caregivers) about the presence of children in the home	○	○	○	○	○
12b	Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	○	○	○	○	○
12c	Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	○	○	○	○	○
12d	Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	○	○	○	○	○
12e	Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	○	○	○	○	○
12f.	Give patients (or their caregivers) the Medication Guide for their TIRF medicine	○	○	○	○	○

13. Please answer True, False, or I don't know for each statement about TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
13a.	TIRF medicines may be sold, loaned, or transferred to another pharmacy.	○	○	○
13b.	All pharmacy staff that dispenses TIRF medicines must be educated on the requirements of the TIRF REMS Access Program.	○	○	○
13c.	TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.	○	○	○

14. **[INPATIENT PHARMACIST]** Does the inpatient pharmacy where you work have an established system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access Program?

- ○ Yes
- ○ No
- ○ I don't know

15. **[OUTPATIENT PHARMACIST]** Does the outpatient or retail pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the pharmacy management system?

- ○ Yes
- ○ No
- ○ I don't know

16. **[CSP OUTPATIENT PHARMACIST]** Does the pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the TIRF REMS Access Call Center?

- ○ Yes
- ○ No
- ○ I don't know

17. **[INPATIENT PHARMACIST]** Please answer True, False, or I don't know for the following statement about TIRF medicines.

	True	False	I don't know
It is OK to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for use at home.	○	○	○

[PREAMBLE 3]

The next set of questions is about the educational materials for TIRF medicines. As a reminder, the TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

18. Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No **[GO TO Q20]**
- ○ I don't know **[GO TO Q20]**

19. Did you read the Full Prescribing Information for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No
- ○ I don't know

20. Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No **[GO TO Q22]**
- ○ I don't know **[GO TO Q22]**

21. Did you read the Medication Guide for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No
- ○ I don't know

22. Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?

- ○ Yes
- ○ No **[GO TO DEMOGRAPHICS PREAMBLE]**
- ○ I don't know **[GO TO DEMOGRAPHICS PREAMBLE]**

23. What are your questions? **[MULTILINE INPUT]**

[DEMOGRAPHICS PREAMBLE]

There are just a few more questions to help us combine your answers with other answers we have received.

24. Are you the Pharmacist in Charge for the TIRF REMS Access Program where you work?

- ○ Yes
- ○ No
- ○ I don't know

25. On average, how many times per month have you dispensed TIRF medicine within the last 6 months?

- ○ None **[Go to DEMOGRAPHICS PREAMBLE 2]**
- ○ 1 – 2 times per month
- ○ 3 – 5 times per month
- ○ More than 5 times per month
- ○ I don't remember

26. Please select the TIRF medicine(s) that you have dispensed within the last 6 months. Please select all that apply.

- ☐ Abstral®
- ☐ Actiq® or generic Actiq®
- ☐ Fentora®
- ☐ Lazanda®
- ☐ Onsolis®
- ☐ Subsys®

[DEMOGRAPHICS PREAMBLE 2]

These last few questions are for demographic purposes.

27. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

28. In total, how many years have you been a practicing pharmacist?

- ○ Less than 3 years
- ○ 3 – 5 years
- ○ 6 – 10 years
- ○ 11 – 15 years
- ○ More than 15 years
- ○ Prefer not to answer

29. In which state do you practice?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" AT END]

[PHONE ONLY: BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- ○ Yes
- ○ No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[CLOSING 1]

We would like to send you a $50 honorarium within the next few weeks to thank you for your time, but we need your name and address to do so. If you do not provide your name and address you will not receive the honorarium for your time and participation in the survey.

Do you agree to give us your name and mailing address so we can send you the honorarium?

- ○ Yes
- ○ No **[SKIP TO CLOSING 2]**

FIRST NAME: **[FREE TEXT]**

LAST NAME: **[FREE TEXT]**

ADDRESS: **[MULTILINE INPUT]**

CITY: **[FREE TEXT]**

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: **[5 NUMERIC CHARACTERS ONLY]**

[CLOSING 2]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

Do you want to provide your telephone number?

- ○ Yes
- ○ No **[SKIP TO CLOSING 3]**

Telephone: **[MUST BE 10-DIGIT NUMERIC CHARACTERS]**

[END CLOSING 2]

[CLOSING 3]

That ends the survey. Thank you again for your help.

[END OF SURVEY CONTENT]

Appendix B SAMPLE Pharmacist Invitation Letter

[CURR_DATE]

[PHARMACY_NAME]

[PHARMACY _STREET_ADDR]
[PHARMACY_CITY], [PHARMACY _STATE] [PHARMACY _ZIP]

[PHARMACY_FAX_NUMBER]

Dear [PHARMACIST_IN CHARGE]

Your Pharmacy was selected to receive this letter, because of enrollment in the TIRF REMS Access Program. We are contacting you to inform you about a survey being conducted by the manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines, as required by the Food and Drug Administration (FDA). The purpose of the survey is to assess pharmacists' understanding of the safe and appropriate use of these medicines. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

The manufacturers of TIRF medicines include Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Meda Pharmaceuticals; Mallinckrodt Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc. (collectively referred to as the "TIRF REMS Industry Group"). These manufacturers are looking for 300 pharmacists to complete the survey. Eligible pharmacists who complete the survey will be sent a $50 honorarium to thank them for their time. The survey will take 15-20 minutes.

Your answers will be kept strictly confidential and will be combined with the answers from other pharmacists who take this survey. Your name will not be used in the report of this survey and your contact information, if provided, will only be used to send you a $50 honorarium for your time to complete the survey.

You are under no obligation to participate in this survey. Only one pharmacist from each enrolled pharmacy can participate. If you are interested in participating and to find out if you are eligible:

- Go to www.TIRFREMSsurvey.com any time or
- Call 1-877-379-3297, 8 a.m. to 8 p.m. Eastern Time, Monday through Friday

Please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**. ***We recommend that you take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.***

Neither taking the survey nor your answers to the questions will affect your ability to dispense any of the TIRF medicines identified above.

Sincerely,

The TIRF REMS Survey Team
1-877-379-3297
www.TIRFREMSsurvey.com

Appendix B Pharmacy Survey Listings and Sub-group Analysis Tables

TABLE 6.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

Sub-group analysis 1: Reading Medication Guide or Full Prescribing Information (Questions 18, 19, 20 and 21):

- **S-1a-Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).**
- **S-1b-Respondents who responded "No" or "I don't know" to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.**

Question	S-1a Read Medication Guide or Full Prescribing Info N=274		S-1b Did not read Medication Guide and Full Prescribing Info N=26	
	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:				
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer				
True [1]	257	93.8 (90.3, 96.3)	24	92.3 (74.9, 99.1)
False	10	3.6	1	3.8
I don't know	7	2.6	1	3.8
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before				
False [1]	239	87.2 (82.7, 90.9)	22	84.6 (65.1, 95.6)
True	26	9.5	3	11.5
I don't know	9	3.3	1	3.8

Question	S-1a Read Medication Guide or Full Prescribing Info N=274		S-1b Did not read Medication Guide and Full Prescribing Info N=26	
	N	% (95% CI)	N	% (95% CI)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy				
False [1]	215	78.5 (73.1, 83.2)	21	80.8 (60.6, 93.4)
True	41	15.0	3	11.5
I don't know	18	6.6	2	7.7
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.				
True [1]	248	90.5 (86.4, 93.7)	24	92.3 (74.9, 99.1)
False	18	6.6	1	3.8
I don't know	8	2.9	1	3.8
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.				
True [1]	257	93.8 (90.3, 96.3)	24	92.3 (74.9, 99.1)
False	4	1.5	0	0.0
I don't know	13	4.7	2	7.7
7c: TIRF medicines may be used in opioid non-tolerant patients.				
False [1]	229	83.6 (78.6, 87.8)	22	84.6 (65.1, 95.6)
True	35	12.8	4	15.4
I don't know	10	3.6	0	0.0

Question	S-1a Read Medication Guide or Full Prescribing Info N=274		S-1b Did not read Medication Guide and Full Prescribing Info N=26	
	N	% (95% CI)	N	% (95% CI)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.				
True [1]	218	79.6 (74.3, 84.2)	19	73.1 (52.2, 88.4)
False	45	16.4	5	19.2
I don't know	11	4.0	2	7.7

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 6.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

Sub-group analysis 1: Reading Medication Guide or Full Prescribing Information (Questions 18, 19, 20 and 21):

- **S-1a-Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).**
- **S-1b-Respondents who responded "No" or "I don't know" to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.**

Demonstrated Understanding	S-1a Read Medication Guide or Full Prescribing Info N=274		S-1b Did not read Medication Guide and Full Prescribing Info N=26	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	1	0.4	1	3.8
2 correct responses	9	3.3	0	0.0
3 correct responses	4	1.5	1	3.8
4 correct responses	14	5.1	1	3.8
5 correct responses	38	13.9	2	7.7
6 correct responses	70	25.5	9	34.6
7 correct responses	138	50.4	12	46.2
Average number of correct responses	6.1 (5.8, 7.0) [1]		6.0 (5.2, 7.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 7.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

Sub-group analysis 1: Reading Medication Guide or Full Prescribing Information (Questions 18, 19, 20 and 21):

- **S-1a-Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).**
- **S-1b-Respondents who responded "No" or "I don't know" to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.**

Question	S-1a Read Medication Guide or Full Prescribing Info N=274		S-1b Did not read Medication Guide and Full Prescribing Info N=26	
	N	% (95% CI)	N	% (95% CI)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.				
9a: Acute or postoperative pain				
No [1]	236	86.1 (81.5, 90.0)	24	92.3 (74.9, 99.1)
Yes	33	12.0	0	0.0
I don't know	5	1.8	2	7.7

Question	S-1a Read Medication Guide or Full Prescribing Info N=274		S-1b Did not read Medication Guide and Full Prescribing Info N=26	
	N	% (95% CI)	N	% (95% CI)
9b: Headache or migraine pain				
No [1]	249	90.9 (86.8, 94.0)	23	88.5 (69.8, 97.6)
Yes	9	3.3	0	0.0
I don't know	16	5.8	3	11.5
9c: Dental pain				
No [1]	266	97.1 (94.3, 98.7)	25	96.2 (80.4, 99.9)
Yes	5	1.8	0	0.0
I don't know	3	1.1	1	3.8
9d: Breakthrough pain from cancer				
Yes [1]	251	91.6 (87.7, 94.6)	24	92.3 (74.9, 99.1)
No	22	8.0	1	3.8
I don't know	1	0.4	1	3.8
9e: Chronic non-cancer pain				
No [1]	122	44.5 (38.5, 50.6)	9	34.6 (17.2, 55.7)
Yes	132	48.2	14	53.8
I don't know	20	7.3	3	11.5

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

Sub-group analysis 1: Reading Medication Guide or Full Prescribing Information (Questions 18, 19, 20 and 21):

- **S-1a-Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).**
- **S-1b-Respondents who responded "No" or "I don't know" to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.**

Demonstrated Understanding	S-1a Read Medication Guide or Full Prescribing Info N=274		S-1b Did not read Medication Guide and Full Prescribing Info N=26	
	N	%	N	%
0 correct responses	1	0.4	0	0.0
1 correct response	6	2.2	1	3.8
2 correct responses	8	2.9	0	0.0
3 correct responses	38	13.9	3	11.5
4 correct responses	117	42.7	15	57.7
5 correct responses	104	38.0	7	26.9
Average number of correct responses	4.1 (3.9, 5.0) [1]		4.0 (3.4, 5.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

Sub-group analysis 1: Reading Medication Guide or Full Prescribing Information (Questions 18, 19, 20 and 21):

- **S-1a-Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).**
- **S-1b-Respondents who responded "No" or "I don't know" to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.**

Question	S-1a Read Medication Guide or Full Prescribing Info N=274		S-1b Did not read Medication Guide and Full Prescribing Info N=26	
	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.				
True [1]	263	96.0 (92.9, 98.0)	25	96.2 (80.4, 99.9)
False	6	2.2	1	3.8
I don't know	5	1.8	0	0.0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.				
8a: A personal history of psychiatric illness				
Yes [1]	196	71.5 (65.8, 76.8)	17	65.4 (44.3, 82.8)
No	44	16.1	2	7.7
I don't know	34	12.4	7	26.9

Question	S-1a Read Medication Guide or Full Prescribing Info N=274		S-1b Did not read Medication Guide and Full Prescribing Info N=26	
	N	% (95% CI)	N	% (95% CI)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse				
Yes [1]	272	99.3 (97.4, 99.9)	26	100.0 (86.8, 100.0)
No	0	0.0	0	0.0
I don't know	2	0.7	0	0.0
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.				
True [1]	258	94.2 (90.7, 96.6)	25	96.2 (80.4, 99.9)
False	11	4.0	1	3.8
I don't know	5	1.8	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

Sub-group analysis 1: Reading Medication Guide or Full Prescribing Information (Questions 18, 19, 20 and 21):

- **S-1a-Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).**
- **S-1b-Respondents who responded "No" or "I don't know" to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.**

Demonstrated Understanding	S-1a Read Medication Guide or Full Prescribing Info N=274		S-1b Did not read Medication Guide and Full Prescribing Info N=26	
	N	%	N	%
0 correct responses	1	0.4	0	0.0
1 correct response	1	0.4	0	0.0
2 correct responses	11	4.0	1	3.8
3 correct responses	78	28.5	9	34.6
4 correct responses	183	66.8	16	61.5
Average number of correct responses	3.6 (3.4, 4.0) [1]		3.6 (3.0, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

Sub-group analysis 1: Reading Medication Guide or Full Prescribing Information (Questions 18, 19, 20 and 21):

- **S-1a-Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).**
- **S-1b-Respondents who responded "No" or "I don't know" to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.**

Question	S-1a Read Medication Guide or Full Prescribing Info N=274		S-1b Did not read Medication Guide and Full Prescribing Info N=26	
	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
10b: TIRF medicines are interchangeable with each other regardless of route of administration.				
False [1]	256	93.4 (89.8, 96.1)	24	92.3 (74.9, 99.1)
True	12	4.4	1	3.8
I don't know	6	2.2	1	3.8
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.				
True [1]	255	93.1 (89.4, 95.8)	24	92.3 (74.9, 99.1)
False	12	4.4	1	3.8
I don't know	7	2.6	1	3.8

Question	S-1a Read Medication Guide or Full Prescribing Info N=274		S-1b Did not read Medication Guide and Full Prescribing Info N=26	
	N	% (95% CI)	N	% (95% CI)
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.				
True [1]	245	89.4 (85.2, 92.8)	25	96.2 (80.4, 99.9)
False	20	7.3	0	0.0
I don't know	9	3.3	1	3.8

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 9.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

Sub-group analysis 1: Reading Medication Guide or Full Prescribing Information (Questions 18, 19, 20 and 21):

- **S-1a-Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).**
- **S-1b-Respondents who responded "No" or "I don't know" to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.**

Demonstrated Understanding	S-1a Read Medication Guide or Full Prescribing Info N=274		S-1b Did not read Medication Guide and Full Prescribing Info N=26	
	N	%	N	%
0 correct responses	3	1.1	0	0.0
1 correct response	8	2.9	1	3.8
2 correct responses	41	15.0	3	11.5
3 correct responses	222	81.0	22	84.6
Average number of correct responses	2.8 (2.6, 3.0) [1]		2.8 (2.3, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 6.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 2: TIME TO COMPLETE SURVEY – INTERNET:

- **S-2a - <10 min**
- **S-2b – 10 to <20 min**
- **S-2c – ≥ 20 min**

Question	S-2a <10 min N=110		S-2b 10 to <20 min N=134		S-2c ≥ 20 min N=43	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:						
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer						
True [1]	104	94.5 (88.5, 98.0)	129	96.3 (91.5, 98.8)	42	97.7 (87.7, 99.9)
False	5	4.5	3	2.2	0	0.0
I don't know	1	0.9	2	1.5	1	2.3
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before						
False [1]	98	89.1 (81.7, 94.2)	120	89.6 (83.1, 94.2)	37	86.0 (72.1, 94.7)
True	9	8.2	12	9.0	4	9.3
I don't know	3	2.7	2	1.5	2	4.7

Question	S-2a <10 min N=110		S-2b 10 to <20 min N=134		S-2c ≥ 20 min N=43	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy						
False [1]	87	79.1 (70.3, 86.3)	106	79.1 (71.2, 85.6)	39	90.7 (77.9, 97.4)
True	18	16.4	20	14.9	2	4.7
I don't know	5	4.5	8	6.0	2	4.7
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.						
True [1]	98	89.1 (81.7, 94.2)	120	89.6 (83.1, 94.2)	42	97.7 (87.7, 99.9)
False	8	7.3	11	8.2	0	0.0
I don't know	4	3.6	3	2.2	1	2.3
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.						
True [1]	102	92.7 (86.2, 96.8)	127	94.8 (89.5, 97.9)	42	97.7 (87.7, 99.9)
False	3	2.7	0	0.0	0	0.0
I don't know	5	4.5	7	5.2	1	2.3
7c: TIRF medicines may be used in opioid non-tolerant patients.						
False [1]	92	83.6 (75.4, 90.0)	109	81.3 (73.7, 87.5)	43	100.0 (91.8, 100.0)
True	12	10.9	22	16.4	0	0.0
I don't know	6	5.5	3	2.2	0	0.0

Question	S-2a <10 min N=110		S-2b 10 to <20 min N=134		S-2c ≥ 20 min N=43	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.						
True [1]	88	80.0 (71.3, 87.0)	100	74.6 (66.4, 81.7)	37	86.0 (72.1, 94.7)
False	14	12.7	29	21.6	6	14.0
I don't know	8	7.3	5	3.7	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 6.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 2: TIME TO COMPLETE SURVEY – INTERNET:

- **S-2a - <10 min**
- **S-2b – 10 to <20 min**
- **S-2c – ≥ 20 min**

Demonstrated Understanding	S-2a <10 min N=110		S-2b 10 to <20 min N=134		S-2c ≥ 20 min N=43	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	1	0.9	1	0.7	0	0.0
2 correct responses	4	3.6	2	1.5	0	0.0
3 correct responses	1	0.9	3	2.2	0	0.0
4 correct responses	4	3.6	8	6.0	1	2.3
5 correct responses	13	11.8	21	15.7	3	7.0
6 correct responses	33	30.0	33	24.6	10	23.3
7 correct responses	54	49.1	66	49.3	29	67.4
Average number of correct responses	6.1 (5.7, 7.0) [1]		6.1 (5.7, 7.0) [1]		6.6 (5.9, 7.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 7.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 2: TIME TO COMPLETE SURVEY – INTERNET:

- **S-2a - <10 min**
- **S-2b – 10 to <20 min**
- **S-2c – ≥ 20 min**

Question	S-2a <10 min N=110		S-2b 10 to <20 min N=134		S-2c ≥ 20 min N=43	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.						
9a: Acute or postoperative pain						
No [1]	91	82.7 (74.3, 89.3)	120	89.6 (83.1, 94.2)	39	90.7 (77.9, 97.4)
Yes	17	15.5	11	8.2	2	4.7
I don't know	2	1.8	3	2.2	2	4.7
9b: Headache or migraine pain						
No [1]	100	90.9 (83.9, 95.6)	118	88.1 (81.3, 93.0)	42	97.7 (87.7, 99.9)
Yes	4	3.6	5	3.7	0	0.0
I don't know	6	5.5	11	8.2	1	2.3

Question	S-2a <10 min N=110		S-2b 10 to <20 min N=134		S-2c ≥ 20 min N=43	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9c: Dental pain						
No [1]	106	96.4 (91.0, 99.0)	132	98.5 (94.7, 99.8)	42	97.7 (87.7, 99.9)
Yes	3	2.7	1	0.7	0	0.0
I don't know	1	0.9	1	0.7	1	2.3
9d: Breakthrough pain from cancer						
Yes [1]	100	90.9 (83.9, 95.6)	122	91.0 (84.9, 95.3)	41	95.3 (84.2, 99.4)
No	9	8.2	11	8.2	2	4.7
I don't know	1	0.9	1	0.7	0	0.0
9e: Chronic non-cancer pain						
No [1]	37	33.6 (24.9, 43.3)	65	48.5 (39.8, 57.3)	22	51.2 (35.5, 66.7)
Yes	61	55.5	61	45.5	19	44.2
I don't know	12	10.9	8	6.0	2	4.7

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 2: TIME TO COMPLETE SURVEY – INTERNET:

- **S-2a - <10 min**
- **S-2b – 10 to <20 min**
- **S-2c – ≥ 20 min**

Demonstrated Understanding	S-2a <10 min N=110		S-2b 10 to <20 min N=134		S-2c ≥ 20 min N=43	
	N	%	N	%	N	%
0 correct responses	1	0.9	0	0.0	0	0.0
1 correct response	3	2.7	2	1.5	1	2.3
2 correct responses	3	2.7	5	3.7	0	0.0
3 correct responses	16	14.5	20	14.9	4	9.3
4 correct responses	58	52.7	50	37.3	17	39.5
5 correct responses	29	26.4	57	42.5	21	48.8
Average number of correct responses	3.9 (3.6, 5.0) [1]		4.2 (3.9, 5.0) [1]		4.3 (3.8, 5.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 2: TIME TO COMPLETE SURVEY – INTERNET:

- **S-2a - <10 min**
- **S-2b – 10 to <20 min**
- **S-2c – ≥ 20 min**

Question	S-2a <10 min N=110		S-2b 10 to <20 min N=134		S-2c ≥ 20 min N=43	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.						
True [1]	104	94.5 (88.5, 98.0)	129	96.3 (91.5, 98.8)	42	97.7 (87.7, 99.9)
False	3	2.7	3	2.2	1	2.3
I don't know	3	2.7	2	1.5	0	0.0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.						
8a: A personal history of psychiatric illness						
Yes [1]	81	73.6 (64.4, 81.6)	88	65.7 (57.0, 73.7)	35	81.4 (66.6, 91.6)
No	16	14.5	24	17.9	3	7.0
I don't know	13	11.8	22	16.4	5	11.6

Question	S-2a <10 min N=110		S-2b 10 to <20 min N=134		S-2c ≥ 20 min N=43	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse						
Yes [1]	109	99.1 (95.0, 100.0)	133	99.3 (95.9, 100.0)	43	100.0 (91.8, 100.0)
No	0	0.0	0	0.0	0	0.0
I don't know	1	0.9	1	0.7	0	0.0
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.						
True [1]	105	95.5 (89.7, 98.5)	126	94.0 (88.6, 97.4)	40	93.0 (80.9, 98.5)
False	4	3.6	5	3.7	3	7.0
I don't know	1	0.9	3	2.2	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 2: TIME TO COMPLETE SURVEY – INTERNET:

- **S-2a - <10 min**
- **S-2b – 10 to <20 min**
- **S-2c – ≥ 20 min**

Demonstrated Understanding	S-2a <10 min N=110		S-2b 10 to <20 min N=134		S-2c ≥ 20 min N=43	
	N	%	N	%	N	%
0 correct responses	1	0.9	0	0.0	0	0.0
1 correct response	0	0.0	1	0.7	0	0.0
2 correct responses	3	2.7	7	5.2	2	4.7
3 correct responses	31	28.2	43	32.1	8	18.6
4 correct responses	75	68.2	83	61.9	33	76.7
Average number of correct responses	3.6 (3.3, 4.0) [1]		3.6 (3.3, 4.0) [1]		3.7 (3.2, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 2: TIME TO COMPLETE SURVEY – INTERNET:

- **S-2a - <10 min**
- **S-2b – 10 to <20 min**
- **S-2c – ≥ 20 min**

Question	S-2a <10 min N=110		S-2b 10 to <20 min N=134		S-2c ≥ 20 min N=43	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
10b: TIRF medicines are interchangeable with each other regardless of route of administration.						
False [1]	102	92.7 (86.2, 96.8)	125	93.3 (87.6, 96.9)	42	97.7 (87.7, 99.9)
True	4	3.6	7	5.2	1	2.3
I don't know	4	3.6	2	1.5	0	0.0
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.						
True [1]	101	91.8 (85.0, 96.2)	124	92.5 (86.7, 96.4)	42	97.7 (87.7, 99.9)
False	6	5.5	6	4.5	1	2.3
I don't know	3	2.7	4	3.0	0	0.0

Question	S-2a <10 min N=110		S-2b 10 to <20 min N=134		S-2c ≥ 20 min N=43	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.						
True [1]	97	88.2 (80.6, 93.6)	123	91.8 (85.8, 95.8)	41	95.3 (84.2, 99.4)
False	10	9.1	5	3.7	2	4.7
I don't know	3	2.7	6	4.5	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 9.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 2: TIME TO COMPLETE SURVEY – INTERNET:

- **S-2a - <10 min**
- **S-2b – 10 to <20 min**
- **S-2c – ≥ 20 min**

Demonstrated Understanding	S-2a <10 min N=110		S-2b 10 to <20 min N=134		S-2c ≥ 20 min N=43	
	N	%	N	%	N	%
0 correct responses	2	1.8	1	0.7	0	0.0
1 correct response	2	1.8	5	3.7	0	0.0
2 correct responses	20	18.2	17	12.7	4	9.3
3 correct responses	86	78.2	111	82.8	39	90.7
Average number of correct responses	2.7 (2.5, 3.0) [1]		2.8 (2.5, 3.0) [1]		2.9 (2.5, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 6.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – TELEPHONE:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Question	S-3a <10 min N=0		S-3b 10 to <20 min N=9		S-3c ≥ 20 min N=4	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:						
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer						
True [1]	0	-	3	33.3 (7.5, 70.1)	3	75.0 (19.4, 99.4)
False	0	-	2	22.2	1	25.0
I don't know	0	-	4	44.4	0	0.0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before						
False [1]	0	-	4	44.4 (13.7, 78.8)	2	50.0 (6.8, 93.2)
True	0	-	2	22.2	2	50.0
I don't know	0	-	3	33.3	0	0.0

Question	S-3a <10 min N=0		S-3b 10 to <20 min N=9		S-3c ≥ 20 min N=4	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy						
False [1]	0	-	3	33.3 (7.5, 70.1)	1	25.0 (0.6, 80.6)
True	0	-	3	33.3	1	25.0
I don't know	0	-	3	33.3	2	50.0
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.						
True [1]	0	-	8	88.9 (51.8, 99.7)	4	100.0 (39.8, 100.0)
False	0	-	0	0.0	0	0.0
I don't know	0	-	1	11.1	0	0.0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.						
True [1]	0	-	8	88.9 (51.8, 99.7)	2	50.0 (6.8, 93.2)
False	0	-	0	0.0	1	25.0
I don't know	0	-	1	11.1	1	25.0
7c: TIRF medicines may be used in opioid non-tolerant patients.						
False [1]	0	-	5	55.6 (21.2, 86.3)	2	50.0 (6.8, 93.2)
True	0	-	3	33.3	2	50.0
I don't know	0	-	1	11.1	0	0.0

Question	S-3a <10 min N=0		S-3b 10 to <20 min N=9		S-3c ≥ 20 min N=4	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.						
True [1]	0	-	8	88.9 (51.8, 99.7)	4	100.0 (39.8, 100.0)
False	0	-	1	11.1	0	0.0
I don't know	0	-	0	0.0	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 6.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – TELEPHONE:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Demonstrated Understanding	S-3a <10 min N=0		S-3b 10 to <20 min N=9		S-3c ≥ 20 min N=4	
	N	%	N	%	N	%
0 correct responses	0	-	0	0.0	0	0.0
1 correct response	0	-	0	0.0	0	0.0
2 correct responses	0	-	3	33.3	0	0.0
3 correct responses	0	-	0	0.0	1	25.0
4 correct responses	0	-	1	11.1	1	25.0
5 correct responses	0	-	2	22.2	1	25.0
6 correct responses	0	-	2	22.2	1	25.0
7 correct responses	0	-	1	11.1	0	0.0
Average number of correct responses	-		4.3 (3.2, 7.0) [1]		4.5 (2.8, 7.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 7.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – TELEPHONE:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Question	S-3a <10 min N=0		S-3b 10 to <20 min N=9		S-3c ≥ 20 min N=4	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.						
9a: Acute or postoperative pain						
No [1]	0	-	6	66.7 (29.9, 92.5)	4	100.0 (39.8, 100.0)
Yes	0	-	3	33.3	0	0.0
I don't know	0	-	0	0.0	0	0.0
9b: Headache or migraine pain						
No [1]	0	-	8	88.9 (51.8, 99.7)	4	100.0 (39.8, 100.0)
Yes	0	-	0	0.0	0	0.0
I don't know	0	-	1	11.1	0	0.0

Question	S-3a <10 min N=0		S-3b 10 to <20 min N=9		S-3c ≥ 20 min N=4	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9c: Dental pain						
No [1]	0	-	7	77.8 (40.0, 97.2)	4	100.0 (39.8, 100.0)
Yes	0	-	1	11.1	0	0.0
I don't know	0	-	1	11.1	0	0.0
9d: Breakthrough pain from cancer						
Yes [1]	0	-	8	88.9 (51.8, 99.7)	4	100.0 (39.8, 100.0)
No	0	-	1	11.1	0	0.0
I don't know	0	-	0	0.0	0	0.0
9e: Chronic non-cancer pain						
No [1]	0	-	4	44.4 (13.7, 78.8)	3	75.0 (19.4, 99.4)
Yes	0	-	4	44.4	1	25.0
I don't know	0	-	1	11.1	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – TELEPHONE:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Demonstrated Understanding	S-3a <10 min N=0		S-3b 10 to <20 min N=9		S-3c ≥ 20 min N=4	
	N	%	N	%	N	%
0 correct responses	0	-	0	0.0	0	0.0
1 correct response	0	-	1	11.1	0	0.0
2 correct responses	0	-	0	0.0	0	0.0
3 correct responses	0	-	1	11.1	0	0.0
4 correct responses	0	-	6	66.7	1	25.0
5 correct responses	0	-	1	11.1	3	75.0
Average number of correct responses	-		3.7 (2.6, 5.0) [1]		4.8 (3.0, 5.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – TELEPHONE:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Question	S-3a <10 min N=0		S-3b 10 to <20 min N=9		S-3c ≥ 20 min N=4	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.						
True [1]	0	-	9	100.0 (66.4, 100.0)	4	100.0 (39.8, 100.0)
False	0	-	0	0.0	0	0.0
I don't know	0	-	0	0.0	0	0.0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.						
8a: A personal history of psychiatric illness						
Yes [1]	0	-	7	77.8 (40.0, 97.2)	2	50.0 (6.8, 93.2)
No	0	-	2	22.2	1	25.0
I don't know	0	-	0	0.0	1	25.0

Question	S-3a <10 min N=0		S-3b 10 to <20 min N=9		S-3c ≥ 20 min N=4	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse						
Yes [1]	0	-	9	100.0 (66.4, 100.0)	4	100.0 (39.8, 100.0)
No	0	-	0	0.0	0	0.0
I don't know	0	-	0	0.0	0	0.0
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.						
True [1]	0	-	8	88.9 (51.8, 99.7)	4	100.0 (39.8, 100.0)
False	0	-	0	0.0	0	0.0
I don't know	0	-	1	11.1	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – TELEPHONE:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Demonstrated Understanding	S-3a <10 min N=0		S-3b 10 to <20 min N=9		S-3c ≥ 20 min N=4	
	N	%	N	%	N	%
0 correct responses	0	-	0	0.0	0	0.0
1 correct response	0	-	0	0.0	0	0.0
2 correct responses	0	-	0	0.0	0	0.0
3 correct responses	0	-	3	33.3	2	50.0
4 correct responses	0	-	6	66.7	2	50.0
Average number of correct responses	-		3.7 (2.6, 4.0) [1]		3.5 (2.0, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – TELEPHONE:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Question	S-3a <10 min N=0		S-3b 10 to <20 min N=9		S-3c ≥ 20 min N=4	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
10b: TIRF medicines are interchangeable with each other regardless of route of administration.						
False [1]	0	-	7	77.8 (40.0, 97.2)	4	100.0 (39.8, 100.0)
True	0	-	1	11.1	0	0.0
I don't know	0	-	1	11.1	0	0.0
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.						
True [1]	0	-	8	88.9 (51.8, 99.7)	4	100.0 (39.8, 100.0)
False	0	-	0	0.0	0	0.0
I don't know	0	-	1	11.1	0	0.0

Question	S-3a <10 min N=0		S-3b 10 to <20 min N=9		S-3c ≥ 20 min N=4	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.						
True [1]	0	-	6	66.7 (29.9, 92.5)	3	75.0 (19.4, 99.4)
False	0	-	2	22.2	1	25.0
I don't know	0	-	1	11.1	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 9.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – TELEPHONE:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Demonstrated Understanding	S-3a <10 min N=0		S-3b 10 to <20 min N=9		S-3c ≥ 20 min N=4	
	N	%	N	%	N	%
0 correct responses	0	-	0	0.0	0	0.0
1 correct response	0	-	2	22.2	0	0.0
2 correct responses	0	-	2	22.2	1	25.0
3 correct responses	0	-	5	55.6	3	75.0
Average number of correct responses	-		2.3 (1.5, 3.0) [1]		2.8 (1.4, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 6.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 4: MODALITY TO COMPLETE SURVEY:

- **S-4a - Internet**
- **S-4b - Telephone**

Question	S-4a Internet N=287		S-4b Telephone N=13	
	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:				
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer				
True [1]	275	95.8 (92.8, 97.8)	6	46.2 (19.2, 74.9)
False	8	2.8	3	23.1
I don't know	4	1.4	4	30.8
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before				
False [1]	255	88.9 (84.6, 92.2)	6	46.2 (19.2, 74.9)
True	25	8.7	4	30.8
I don't know	7	2.4	3	23.1
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy				
False [1]	232	80.8 (75.8, 85.2)	4	30.8 (9.1, 61.4)
True	40	13.9	4	30.8
I don't know	15	5.2	5	38.5

Question	S-4a Internet N=287		S-4b Telephone N=13	
	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.				
True [1]	260	90.6 (86.6, 93.7)	12	92.3 (64.0, 99.8)
False	19	6.6	0	0.0
I don't know	8	2.8	1	7.7
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.				
True [1]	271	94.4 (91.1, 96.8)	10	76.9 (46.2, 95.0)
False	3	1.0	1	7.7
I don't know	13	4.5	2	15.4
7c: TIRF medicines may be used in opioid non-tolerant patients.				
False [1]	244	85.0 (80.4, 88.9)	7	53.8 (25.1, 80.8)
True	34	11.8	5	38.5
I don't know	9	3.1	1	7.7
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.				
True [1]	225	78.4 (73.2, 83.0)	12	92.3 (64.0, 99.8)
False	49	17.1	1	7.7
I don't know	13	4.5	0	0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 6.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 4: MODALITY TO COMPLETE SURVEY:

- **S-4a - Internet**
- **S-4b - Telephone**

Demonstrated Understanding	S-4a Internet N=287		S-4b Telephone N=13	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	2	0.7	0	0.0
2 correct responses	6	2.1	3	23.1
3 correct responses	4	1.4	1	7.7
4 correct responses	13	4.5	2	15.4
5 correct responses	37	12.9	3	23.1
6 correct responses	76	26.5	3	23.1
7 correct responses	149	51.9	1	7.7
Average number of correct responses	6.1 (5.9, 7.0) [1]		4.4 (3.4, 7.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 7.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 4: MODALITY TO COMPLETE SURVEY:

- **S-4a - Internet**
- **S-4b - Telephone**

Question	S-4a Internet N=287		S-4b Telephone N=13	
	N	% (95% CI)	N	% (95% CI)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.				
9a: Acute or postoperative pain				
No [1]	250	87.1 (82.7, 90.8)	10	76.9 (46.2, 95.0)
Yes	30	10.5	3	23.1
I don't know	7	2.4	0	0.0
9b: Headache or migraine pain				
No [1]	260	90.6 (86.6, 93.7)	12	92.3 (64.0, 99.8)
Yes	9	3.1	0	0.0
I don't know	18	6.3	1	7.7

Question	S-4a Internet N=287		S-4b Telephone N=13	
	N	% (95% CI)	N	% (95% CI)
9c: Dental pain				
No [1]	280	97.6 (95.0, 99.0)	11	84.6 (54.6, 98.1)
Yes	4	1.4	1	7.7
I don't know	3	1.0	1	7.7
9d: Breakthrough pain from cancer				
Yes [1]	263	91.6 (87.8, 94.6)	12	92.3 (64.0, 99.8)
No	22	7.7	1	7.7
I don't know	2	0.7	0	0.0
9e: Chronic non-cancer pain				
No [1]	124	43.2 (37.4, 49.2)	7	53.8 (25.1, 80.8)
Yes	141	49.1	5	38.5
I don't know	22	7.7	1	7.7

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 4: MODALITY TO COMPLETE SURVEY:

- **S-4a - Internet**
- **S-4b - Telephone**

Demonstrated Understanding	S-4a Internet N=287		S-4b Telephone N=13	
	N	%	N	%
0 correct responses	1	0.3	0	0.0
1 correct response	6	2.1	1	7.7
2 correct responses	8	2.8	0	0.0
3 correct responses	40	13.9	1	7.7
4 correct responses	125	43.6	7	53.8
5 correct responses	107	37.3	4	30.8
Average number of correct responses	4.1 (3.9, 5.0) [1]		4.0 (3.1, 5.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 4: MODALITY TO COMPLETE SURVEY:

- **S-4a - Internet**
- **S-4b - Telephone**

Question	S-4a Internet N=287		S-4b Telephone N=13	
	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.				
True [1]	275	95.8 (92.8, 97.8)	13	100.0 (75.3, 100.0)
False	7	2.4	0	0.0
I don't know	5	1.7	0	0.0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.				
8a: A personal history of psychiatric illness				
Yes [1]	204	71.1 (65.5, 76.3)	9	69.2 (38.6, 90.9)
No	43	15.0	3	23.1
I don't know	40	13.9	1	7.7

Question	S-4a Internet N=287		S-4b Telephone N=13	
	N	% (95% CI)	N	% (95% CI)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse				
Yes [1]	285	99.3 (97.5, 99.9)	13	100.0 (75.3, 100.0)
No	0	0.0	0	0.0
I don't know	2	0.7	0	0.0
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.				
True [1]	271	94.4 (91.1, 96.8)	12	92.3 (64.0, 99.8)
False	12	4.2	0	0.0
I don't know	4	1.4	1	7.7

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 4: MODALITY TO COMPLETE SURVEY:

- **S-4a - Internet**
- **S-4b - Telephone**

Demonstrated Understanding	S-4a Internet N=287		S-4b Telephone N=13	
	N	%	N	%
0 correct responses	1	0.3	0	0.0
1 correct response	1	0.3	0	0.0
2 correct responses	12	4.2	0	0.0
3 correct responses	82	28.6	5	38.5
4 correct responses	191	66.6	8	61.5
Average number of correct responses	3.6 (3.4, 4.0) [1]		3.6 (2.7, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 4: MODALITY TO COMPLETE SURVEY:

- **S-4a - Internet**
- **S-4b - Telephone**

Question	S-4a Internet N=287		S-4b Telephone N=13	
	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
10b: TIRF medicines are interchangeable with each other regardless of route of administration.				
False [1]	269	93.7 (90.3, 96.2)	11	84.6 (54.6, 98.1)
True	12	4.2	1	7.7
I don't know	6	2.1	1	7.7
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.				
True [1]	267	93.0 (89.4, 95.7)	12	92.3 (64.0, 99.8)
False	13	4.5	0	0.0
I don't know	7	2.4	1	7.7
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.				
True [1]	261	90.9 (87.0, 94.0)	9	69.2 (38.6, 90.9)
False	17	5.9	3	23.1
I don't know	9	3.1	1	7.7

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 9.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 4: MODALITY TO COMPLETE SURVEY:

- **S-4a - Internet**
- **S-4b - Telephone**

Demonstrated Understanding	S-4a Internet N=287		S-4b Telephone N=13	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	3	1.0	0	0.0
1 correct response	7	2.4	2	15.4
2 correct responses	41	14.3	3	23.1
3 correct responses	236	82.2	8	61.5
Average number of correct responses	2.8 (2.6, 3.0) [1]		2.5 (1.7, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 6.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 5: TIME PRACTICING AS A PHARMACIST (QUESTION 28):

- **S-5a - Less than 3 years**
- **S-5b - 3 to 5 years**
- **S-5c - 6 to 15 years**
- **S-5d - More than 15 years**

Question	S-5a Less than 3 years N=16		S-5b 3 to 5 years N=28		S-5c 6 to 15 years N=102		S-5d More than 15 years N=150	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:								
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer								
True [1]	15	93.8 (69.8, 99.8)	27	96.4 (81.7, 99.9)	92	90.2 (82.7, 95.2)	143	95.3 (90.6, 98.1)
False	0	0.0	1	3.6	6	5.9	4	2.7
I don't know	1	6.3	0	0.0	4	3.9	3	2.0

Question	S-5a Less than 3 years N=16		S-5b 3 to 5 years N=28		S-5c 6 to 15 years N=102		S-5d More than 15 years N=150	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before								
False [1]	15	93.8 (69.8, 99.8)	26	92.9 (76.5, 99.1)	88	86.3 (78.0, 92.3)	129	86.0 (79.4, 91.1)
True	0	0.0	2	7.1	9	8.8	17	11.3
I don't know	1	6.3	0	0.0	5	4.9	4	2.7
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy								
False [1]	13	81.3 (54.4, 96.0)	24	85.7 (67.3, 96.0)	82	80.4 (71.4, 87.6)	114	76.0 (68.4, 82.6)
True	1	6.3	3	10.7	12	11.8	27	18.0
I don't know	2	12.5	1	3.6	8	7.8	9	6.0
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.								
True [1]	14	87.5 (61.7, 98.4)	28	100.0 (87.7, 100.0)	95	93.1 (86.4, 97.2)	132	88.0 (81.7, 92.7)
False	2	12.5	0	0.0	4	3.9	13	8.7
I don't know	0	0.0	0	0.0	3	2.9	5	3.3
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.								

Question	S-5a Less than 3 years N=16		S-5b 3 to 5 years N=28		S-5c 6 to 15 years N=102		S-5d More than 15 years N=150	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
True [1]	15	93.8 (69.8, 99.8)	27	96.4 (81.7, 99.9)	98	96.1 (90.3, 98.9)	138	92.0 (86.4, 95.8)
False	0	0.0	0	0.0	1	1.0	3	2.0
I don't know	1	6.3	1	3.6	3	2.9	9	6.0
7c: TIRF medicines may be used in opioid non-tolerant patients.								
False [1]	15	93.8 (69.8, 99.8)	28	100.0 (87.7, 100.0)	88	86.3 (78.0, 92.3)	117	78.0 (70.5, 84.3)
True	0	0.0	0	0.0	11	10.8	28	18.7
I don't know	1	6.3	0	0.0	3	2.9	5	3.3
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.								
True [1]	14	87.5 (61.7, 98.4)	25	89.3 (71.8, 97.7)	85	83.3 (74.7, 90.0)	110	73.3 (65.5, 80.2)
False	2	12.5	3	10.7	13	12.7	32	21.3
I don't know	0	0.0	0	0.0	4	3.9	8	5.3

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 6.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 5: TIME PRACTICING AS A PHARMACIST (QUESTION 28):

- **S-5a - Less than 3 years**
- **S-5b - 3 to 5 years**
- **S-5c - 6 to 15 years**
- **S-5d - More than 15 years**

Demonstrated Understanding	S-5a Less than 3 years N=16		S-5b 3 to 5 years N=28		S-5c 6 to 15 years N=102		S-5d More than 15 years N=150	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	1	1.0	1	0.7
2 correct responses	1	6.3	0	0.0	2	2.0	6	4.0
3 correct responses	0	0.0	0	0.0	1	1.0	3	2.0
4 correct responses	0	0.0	0	0.0	6	5.9	9	6.0
5 correct responses	0	0.0	1	3.6	12	11.8	26	17.3
6 correct responses	6	37.5	9	32.1	24	23.5	40	26.7
7 correct responses	9	56.3	18	64.3	56	54.9	65	43.3
Average number of correct responses	6.3 (5.3, 7.0) [1]		6.6 (5.8, 7.0) [1]		6.2 (5.8, 7.0) [1]		5.9 (5.6, 7.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

Client: TRIG Project: TIRF Wave 3

Report Run Date and Time: 10/14/2014 1:55 PM

TABLE 7.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 5: TIME PRACTICING AS A PHARMACIST (QUESTION 28):

- **S-5a - Less than 3 years**
- **S-5b - 3 to 5 years**
- **S-5c - 6 to 15 years**
- **S-5d - More than 15 years**

Question	S-5a Less than 3 years N=16		S-5b 3 to 5 years N=28		S-5c 6 to 15 years N=102		S-5d More than 15 years N=150	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.								
9a: Acute or postoperative pain								
No [1]	12	75.0 (47.6, 92.7)	26	92.9 (76.5, 99.1)	93	91.2 (83.9, 95.9)	128	85.3 (78.6, 90.6)
Yes	2	12.5	2	7.1	8	7.8	20	13.3
I don't know	2	12.5	0	0.0	1	1.0	2	1.3

Question	S-5a Less than 3 years N=16		S-5b 3 to 5 years N=28		S-5c 6 to 15 years N=102		S-5d More than 15 years N=150	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9b: Headache or migraine pain								
No [1]	13	81.3 (54.4, 96.0)	27	96.4 (81.7, 99.9)	96	94.1 (87.6, 97.8)	133	88.7 (82.5, 93.3)
Yes	0	0.0	0	0.0	0	0.0	9	6.0
I don't know	3	18.8	1	3.6	6	5.9	8	5.3
9c: Dental pain								
No [1]	14	87.5 (61.7, 98.4)	28	100.0 (87.7, 100.0)	100	98.0 (93.1, 99.8)	146	97.3 (93.3, 99.3)
Yes	0	0.0	0	0.0	1	1.0	4	2.7
I don't know	2	12.5	0	0.0	1	1.0	0	0.0
9d: Breakthrough pain from cancer								
Yes [1]	14	87.5 (61.7, 98.4)	28	100.0 (87.7, 100.0)	88	86.3 (78.0, 92.3)	142	94.7 (89.8, 97.7)
No	2	12.5	0	0.0	13	12.7	8	5.3
I don't know	0	0.0	0	0.0	1	1.0	0	0.0

Question	S-5a Less than 3 years N=16		S-5b 3 to 5 years N=28		S-5c 6 to 15 years N=102		S-5d More than 15 years N=150	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9e: Chronic non-cancer pain								
No [1]	8	50.0 (24.7, 75.3)	11	39.3 (21.5, 59.4)	46	45.1 (35.2, 55.3)	66	44.0 (35.9, 52.3)
Yes	4	25.0	15	53.6	47	46.1	78	52.0
I don't know	4	25.0	2	7.1	9	8.8	6	4.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 5: TIME PRACTICING AS A PHARMACIST (QUESTION 28):

- **S-5a - Less than 3 years**
- **S-5b - 3 to 5 years**
- **S-5c - 6 to 15 years**
- **S-5d - More than 15 years**

Demonstrated Understanding	S-5a Less than 3 years N=16		S-5b 3 to 5 years N=28		S-5c 6 to 15 years N=102		S-5d More than 15 years N=150	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	2	12.5	0	0.0	2	2.0	3	2.0
2 correct responses	1	6.3	1	3.6	0	0.0	6	4.0
3 correct responses	2	12.5	1	3.6	15	14.7	21	14.0
4 correct responses	4	25.0	15	53.6	49	48.0	63	42.0
5 correct responses	7	43.8	11	39.3	36	35.3	57	38.0

Demonstrated Understanding	S-5a Less than 3 years N=16		S-5b 3 to 5 years N=28		S-5c 6 to 15 years N=102		S-5d More than 15 years N=150	
	N	%	N	%	N	%	N	%
Average number of correct responses	3.8 (3.0, 5.0) [1]		4.3 (3.6, 5.0) [1]		4.1 (3.8, 5.0) [1]		4.1 (3.8, 5.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 5: TIME PRACTICING AS A PHARMACIST (QUESTION 28):

- **S-5a - Less than 3 years**
- **S-5b - 3 to 5 years**
- **S-5c - 6 to 15 years**
- **S-5d - More than 15 years**

Question	S-5a Less than 3 years N=16		S-5b 3 to 5 years N=28		S-5c 6 to 15 years N=102		S-5d More than 15 years N=150	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.								
True [1]	16	100.0 (79.4, 100.0)	28	100.0 (87.7, 100.0)	100	98.0 (93.1, 99.8)	141	94.0 (88.9, 97.2)
False	0	0.0	0	0.0	0	0.0	7	4.7
I don't know	0	0.0	0	0.0	2	2.0	2	1.3

Question	S-5a Less than 3 years N=16		S-5b 3 to 5 years N=28		S-5c 6 to 15 years N=102		S-5d More than 15 years N=150	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.								
8a: A personal history of psychiatric illness								
Yes [1]	9	56.3 (29.9, 80.2)	25	89.3 (71.8, 97.7)	74	72.5 (62.8, 80.9)	103	68.7 (60.6, 76.0)
No	3	18.8	3	10.7	14	13.7	25	16.7
I don't know	4	25.0	0	0.0	14	13.7	22	14.7
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse								
Yes [1]	16	100.0 (79.4, 100.0)	28	100.0 (87.7, 100.0)	101	99.0 (94.7, 100.0)	150	100.0 (97.6, 100.0)
No	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	1	1.0	0	0.0

Question	S-5a Less than 3 years N=16 [1]		S-5b 3 to 5 years N=28 [1]		S-5c 6 to 15 years N=102 [1]		S-5d More than 15 years N=150 [1]	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.								
True [1]	14	87.5 (61.7, 98.4)	27	96.4 (81.7, 99.9)	96	94.1 (87.6, 97.8)	143	95.3 (90.6, 98.1)
False	1	6.3	1	3.6	3	2.9	7	4.7
I don't know	1	6.3	0	0.0	3	2.9	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 5: TIME PRACTICING AS A PHARMACIST (QUESTION 28):

- **S-5a - Less than 3 years**
- **S-5b - 3 to 5 years**
- **S-5c - 6 to 15 years**
- **S-5d - More than 15 years**

Demonstrated Understanding	S-5a Less than 3 years N=16		S-5b 3 to 5 years N=28		S-5c 6 to 15 years N=102		S-5d More than 15 years N=150	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	1	1.0	0	0.0
2 correct responses	0	0.0	0	0.0	3	2.9	9	6.0
3 correct responses	9	56.3	4	14.3	28	27.5	45	30.0
4 correct responses	7	43.8	24	85.7	70	68.6	96	64.0
Average number of correct responses	3.4 (2.7, 4.0) [1]		3.9 (3.2, 4.0) [1]		3.6 (3.3, 4.0) [1]		3.6 (3.3, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 5: TIME PRACTICING AS A PHARMACIST (QUESTION 28):

- **S-5a - Less than 3 years**
- **S-5b - 3 to 5 years**
- **S-5c - 6 to 15 years**
- **S-5d - More than 15 years**

Question	S-5a Less than 3 years N=16		S-5b 3 to 5 years N=28		S-5c 6 to 15 years N=102		S-5d More than 15 years N=150	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
10b: TIRF medicines are interchangeable with each other regardless of route of administration.								
False [1]	15	93.8 (69.8, 99.8)	28	100.0 (87.7, 100.0)	96	94.1 (87.6, 97.8)	138	92.0 (86.4, 95.8)
True	1	6.3	0	0.0	4	3.9	8	5.3
I don't know	0	0.0	0	0.0	2	2.0	4	2.7

Question	S-5a Less than 3 years N=16		S-5b 3 to 5 years N=28		S-5c 6 to 15 years N=102		S-5d More than 15 years N=150	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.								
True [1]	16	100.0 (79.4, 100.0)	28	100.0 (87.7, 100.0)	98	96.1 (90.3, 98.9)	134	89.3 (83.3, 93.8)
False	0	0.0	0	0.0	1	1.0	12	8.0
I don't know	0	0.0	0	0.0	3	2.9	4	2.7
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.								
True [1]	16	100.0 (79.4, 100.0)	27	96.4 (81.7, 99.9)	91	89.2 (81.5, 94.5)	133	88.7 (82.5, 93.3)
False	0	0.0	1	3.6	9	8.8	10	6.7
I don't know	0	0.0	0	0.0	2	2.0	7	4.7

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 9.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 5: TIME PRACTICING AS A PHARMACIST (QUESTION 28):

- **S-5a - Less than 3 years**
- **S-5b - 3 to 5 years**
- **S-5c - 6 to 15 years**
- **S-5d - More than 15 years**

Demonstrated Understanding	S-5a Less than 3 years N=16		S-5b 3 to 5 years N=28		S-5c 6 to 15 years N=102		S-5d More than 15 years N=150	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	1	1.0	1	0.7
1 correct response	0	0.0	0	0.0	2	2.0	7	4.7
2 correct responses	1	6.3	1	3.6	14	13.7	28	18.7
3 correct responses	15	93.8	27	96.4	85	83.3	114	76.0
Average number of correct responses	2.9 (2.2, 3.0) [1]		3.0 (2.4, 3.0) [1]		2.8 (2.5, 3.0) [1]		2.7 (2.5, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 6.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSED TIRF MEDICINE WITHIN THE LAST 6 MONTHS (QUESTION 25):

- **S-6a - None**
- **S-6b - 1 - 2 times per month**
- **S-6c - 3 - 5 times per month**
- **S-6d - More than 5 times per month**

Question	S-6a None N=132		S-6b 1 - 2 times per month N=81		S-6c 3 - 5 times per month N=36		S-6d More than 5 times per month N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:								
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer								
True [1]	122	92.4 (86.5, 96.3)	76	93.8 (86.2, 98.0)	34	94.4 (81.3, 99.3)	30	96.8 (83.3, 99.9)
False	6	4.5	3	3.7	1	2.8	0	0.0
I don't know	4	3.0	2	2.5	1	2.8	1	3.2

Question	S-6a None N=132		S-6b 1 - 2 times per month N=81		S-6c 3 - 5 times per month N=36		S-6d More than 5 times per month N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before								
False [1]	115	87.1 (80.2, 92.3)	69	85.2 (75.6, 92.1)	28	77.8 (60.8, 89.9)	29	93.5 (78.6, 99.2)
True	14	10.6	9	11.1	5	13.9	1	3.2
I don't know	3	2.3	3	3.7	3	8.3	1	3.2
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy								
False [1]	108	81.8 (74.2, 88.0)	62	76.5 (65.8, 85.2)	25	69.4 (51.9, 83.7)	24	77.4 (58.9, 90.4)
True	14	10.6	14	17.3	8	22.2	6	19.4
I don't know	10	7.6	5	6.2	3	8.3	1	3.2
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.								
True [1]	123	93.2 (87.5, 96.8)	67	82.7 (72.7, 90.2)	31	86.1 (70.5, 95.3)	31	100.0 (88.8, 100.0)
False	5	3.8	11	13.6	3	8.3	0	0.0
I don't know	4	3.0	3	3.7	2	5.6	0	0.0

Question	S-6a None N=132		S-6b 1 - 2 times per month N=81		S-6c 3 - 5 times per month N=36		S-6d More than 5 times per month N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.								
True [1]	122	92.4 (86.5, 96.3)	75	92.6 (84.6, 97.2)	34	94.4 (81.3, 99.3)	31	100.0 (88.8, 100.0)
False	1	0.8	3	3.7	0	0.0	0	0.0
I don't know	9	6.8	3	3.7	2	5.6	0	0.0
7c: TIRF medicines may be used in opioid non-tolerant patients.								
False [1]	112	84.8 (77.6, 90.5)	64	79.0 (68.5, 87.3)	27	75.0 (57.8, 87.9)	28	90.3 (74.2, 98.0)
True	15	11.4	13	16.0	8	22.2	3	9.7
I don't know	5	3.8	4	4.9	1	2.8	0	0.0

Question	S-6a None N=132 [1]		S-6b 1 - 2 times per month N=81 [1]		S-6c 3 - 5 times per month N=36 [1]		S-6d More than 5 times per month N=31 [1]	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.								
True [1]	112	84.8 (77.6, 90.5)	59	72.8 (61.8, 82.1)	27	75.0 (57.8, 87.9)	23	74.2 (55.4, 88.1)
False	16	12.1	15	18.5	8	22.2	8	25.8
I don't know	4	3.0	7	8.6	1	2.8	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 6.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSED TIRF MEDICINE WITHIN THE LAST 6 MONTHS (QUESTION 25):

- **S-6a - None**
- **S-6b - 1 - 2 times per month**
- **S-6c - 3 - 5 times per month**
- **S-6d - More than 5 times per month**

Demonstrated Understanding	S-6a None N=132		S-6b 1 - 2 times per month N=81		S-6c 3 - 5 times per month N=36		S-6d More than 5 times per month N=31	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	1	0.8	0	0.0	1	2.8	0	0.0
2 correct responses	4	3.0	4	4.9	1	2.8	0	0.0
3 correct responses	2	1.5	3	3.7	0	0.0	0	0.0
4 correct responses	5	3.8	8	9.9	2	5.6	0	0.0
5 correct responses	16	12.1	9	11.1	9	25.0	3	9.7
6 correct responses	29	22.0	21	25.9	11	30.6	15	48.4
7 correct responses	75	56.8	36	44.4	12	33.3	13	41.9

Demonstrated Understanding	S-6a None N=132		S-6b 1 - 2 times per month N=81		S-6c 3 - 5 times per month N=36		S-6d More than 5 times per month N=31	
	N	%	N	%	N	%	N	%
Average number of correct responses	6.2 (5.8, 7.0) [1]		5.8 (5.4, 7.0) [1]		5.7 (5.1, 7.0) [1]		6.3 (5.6, 7.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 7.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSED TIRF MEDICINE WITHIN THE LAST 6 MONTHS (QUESTION 25):

- **S-6a - None**
- **S-6b - 1 - 2 times per month**
- **S-6c - 3 - 5 times per month**
- **S-6d - More than 5 times per month**

Question	S-6a None N=132		S-6b 1 - 2 times per month N=81		S-6c 3 - 5 times per month N=36		S-6d More than 5 times per month N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.								
9a: Acute or postoperative pain								
No [1]	116	87.9 (81.1, 92.9)	66	81.5 (71.3, 89.2)	32	88.9 (73.9, 96.9)	27	87.1 (70.2, 96.4)
Yes	11	8.3	13	16.0	4	11.1	4	12.9
I don't know	5	3.8	2	2.5	0	0.0	0	0.0
9b: Headache or migraine pain								
No [1]	121	91.7 (85.6, 95.8)	72	88.9 (80.0, 94.8)	31	86.1 (70.5, 95.3)	29	93.5 (78.6, 99.2)
Yes	4	3.0	3	3.7	1	2.8	1	3.2
I don't know	7	5.3	6	7.4	4	11.1	1	3.2
9c: Dental pain								
No [1]	128	97.0 (92.4, 99.2)	78	96.3 (89.6, 99.2)	34	94.4 (81.3, 99.3)	31	100.0 (88.8, 100.0)
Yes	1	0.8	2	2.5	2	5.6	0	0.0
I don't know	3	2.3	1	1.2	0	0.0	0	0.0

Question	S-6a None N=132		S-6b 1 - 2 times per month N=81		S-6c 3 - 5 times per month N=36		S-6d More than 5 times per month N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9d: Breakthrough pain from cancer								
Yes [1]	121	91.7 (85.6, 95.8)	76	93.8 (86.2, 98.0)	31	86.1 (70.5, 95.3)	27	87.1 (70.2, 96.4)
No	10	7.6	4	4.9	5	13.9	4	12.9
I don't know	1	0.8	1	1.2	0	0.0	0	0.0
9e: Chronic non-cancer pain								
No [1]	52	39.4 (31.0, 48.3)	40	49.4 (38.1, 60.7)	15	41.7 (25.5, 59.2)	12	38.7 (21.8, 57.8)
Yes	66	50.0	38	46.9	18	50.0	17	54.8
I don't know	14	10.6	3	3.7	3	8.3	2	6.5

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSED TIRF MEDICINE WITHIN THE LAST 6 MONTHS (QUESTION 25):

- **S-6a - None**
- **S-6b - 1 - 2 times per month**
- **S-6c - 3 - 5 times per month**
- **S-6d - More than 5 times per month**

Demonstrated Understanding	S-6a None N=132		S-6b 1 - 2 times per month N=81		S-6c 3 - 5 times per month N=36		S-6d More than 5 times per month N=31	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	1	1.2	0	0.0	0	0.0
1 correct response	4	3.0	2	2.5	1	2.8	0	0.0
2 correct responses	2	1.5	3	3.7	1	2.8	2	6.5
3 correct responses	16	12.1	10	12.3	7	19.4	6	19.4
4 correct responses	68	51.5	31	38.3	16	44.4	11	35.5

Demonstrated Understanding	S-6a None N=132		S-6b 1 - 2 times per month N=81		S-6c 3 - 5 times per month N=36		S-6d More than 5 times per month N=31	
	N	%	N	%	N	%	N	%
5 correct responses	42	31.8	34	42.0	11	30.6	12	38.7
Average number of correct responses	4.1 (3.8, 5.0) [1]		4.1 (3.7, 5.0) [1]		4.0 (3.4, 5.0) [1]		4.1 (3.5, 5.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSED TIRF MEDICINE WITHIN THE LAST 6 MONTHS (QUESTION 25):

- **S-6a - None**
- **S-6b - 1 - 2 times per month**
- **S-6c - 3 - 5 times per month**
- **S-6d - More than 5 times per month**

Question	S-6a None N=132		S-6b 1 - 2 times per month N=81		S-6c 3 - 5 times per month N=36		S-6d More than 5 times per month N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.								
True [1]	127	96.2 (91.4, 98.8)	78	96.3 (89.6, 99.2)	33	91.7 (77.5, 98.2)	31	100.0 (88.8, 100.0)
False	3	2.3	2	2.5	1	2.8	0	0.0
I don't know	2	1.5	1	1.2	2	5.6	0	0.0

Question	S-6a None N=132		S-6b 1 - 2 times per month N=81		S-6c 3 - 5 times per month N=36		S-6d More than 5 times per month N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.								
8a: A personal history of psychiatric illness								
Yes [1]	96	72.7 (64.3, 80.1)	56	69.1 (57.9, 78.9)	23	63.9 (46.2, 79.2)	25	80.6 (62.5, 92.5)
No	20	15.2	13	16.0	8	22.2	2	6.5
I don't know	16	12.1	12	14.8	5	13.9	4	12.9
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse								
Yes [1]	132	100.0 (97.2, 100.0)	80	98.8 (93.3, 100.0)	36	100.0 (90.3, 100.0)	30	96.8 (83.3, 99.9)
No	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	1	1.2	0	0.0	1	3.2

Question	S-6a None N=132 [1]		S-6b 1 - 2 times per month N=81 [1]		S-6c 3 - 5 times per month N=36 [1]		S-6d More than 5 times per month N=31 [1]	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.								
True [1]	127	96.2 (91.4, 98.8)	74	91.4 (83.0, 96.5)	35	97.2 (85.5, 99.9)	28	90.3 (74.2, 98.0)
False	2	1.5	6	7.4	1	2.8	2	6.5
I don't know	3	2.3	1	1.2	0	0.0	1	3.2

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSED TIRF MEDICINE WITHIN THE LAST 6 MONTHS (QUESTION 25):

- **S-6a - None**
- **S-6b - 1 - 2 times per month**
- **S-6c - 3 - 5 times per month**
- **S-6d - More than 5 times per month**

Demonstrated Understanding	S-6a None N=132		S-6b 1 - 2 times per month N=81		S-6c 3 - 5 times per month N=36		S-6d More than 5 times per month N=31	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	1	1.2	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	0	0.0	1	3.2
2 correct responses	5	3.8	2	2.5	2	5.6	1	3.2
3 correct responses	36	27.3	28	34.6	13	36.1	5	16.1
4 correct responses	91	68.9	50	61.7	21	58.3	24	77.4

Demonstrated Understanding	S-6a None N=132		S-6b 1 - 2 times per month N=81		S-6c 3 - 5 times per month N=36		S-6d More than 5 times per month N=31	
	N	%	N	%	N	%	N	%
Average number of correct responses	3.7 (3.4, 4.0) [1]		3.6 (3.2, 4.0) [1]		3.5 (3.0, 4.0) [1]		3.7 (3.1, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSED TIRF MEDICINE WITHIN THE LAST 6 MONTHS (QUESTION 25):

- **S-6a - None**
- **S-6b - 1 - 2 times per month**
- **S-6c - 3 - 5 times per month**
- **S-6d - More than 5 times per month**

Question	S-6a None N=132		S-6b 1 - 2 times per month N=81		S-6c 3 - 5 times per month N=36		S-6d More than 5 times per month N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
10b: TIRF medicines are interchangeable with each other regardless of route of administration.								
False [1]	127	96.2 (91.4, 98.8)	72	88.9 (80.0, 94.8)	35	97.2 (85.5, 99.9)	28	90.3 (74.2, 98.0)
True	4	3.0	6	7.4	1	2.8	1	3.2
I don't know	1	0.8	3	3.7	0	0.0	2	6.5
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the								

Question	S-6a None N=132		S-6b 1 - 2 times per month N=81		S-6c 3 - 5 times per month N=36		S-6d More than 5 times per month N=31	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
pharmacokinetics of fentanyl absorption.								
True [1]	123	93.2 (87.5, 96.8)	74	91.4 (83.0, 96.5)	33	91.7 (77.5, 98.2)	30	96.8 (83.3, 99.9)
False	5	3.8	6	7.4	0	0.0	1	3.2
I don't know	4	3.0	1	1.2	3	8.3	0	0.0
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.								
True [1]	119	90.2 (83.7, 94.7)	74	91.4 (83.0, 96.5)	31	86.1 (70.5, 95.3)	31	100.0 (88.8, 100.0)
False	9	6.8	5	6.2	4	11.1	0	0.0
I don't know	4	3.0	2	2.5	1	2.8	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 9.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSED TIRF MEDICINE WITHIN THE LAST 6 MONTHS (QUESTION 25):

- **S-6a - None**
- **S-6b - 1 - 2 times per month**
- **S-6c - 3 - 5 times per month**
- **S-6d - More than 5 times per month**

Demonstrated Understanding	S-6a None N=132		S-6b 1 - 2 times per month N=81		S-6c 3 - 5 times per month N=36		S-6d More than 5 times per month N=31	
	N	%	N	%	N	%	N	%
0 correct responses	1	0.8	1	1.2	0	0.0	0	0.0
1 correct response	3	2.3	3	3.7	3	8.3	0	0.0
2 correct responses	18	13.6	14	17.3	3	8.3	4	12.9
3 correct responses	110	83.3	63	77.8	30	83.3	27	87.1
Average number of correct responses	2.8 (2.6, 3.0) [1]		2.7 (2.4, 3.0) [1]		2.8 (2.3, 3.0) [1]		2.9 (2.4, 3.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

Listing 1

VERBATIM RESPONSES TO REPORTED ADVERSE EVENTS, PRODUCT COMPLAINTS OR REQUESTS FOR MEDICAL INFORMATION

Verbatim Response
Are there other opioid-type medications with which TIRF pain-management medications should not be used?
Are these for any specific kind of cancer or for any type of cancer?
can you put an easy chart and app together?
HOW DO YOU PREVENT AN OVERDOSE WITH PATIENTS WHO ARE IN SO MUCH PAIN, AND FAMILY MEMBERS WHO ARE TOO INVOLVED AND JUST WANT TO SEE THE PATIENT BE PAIN FREE?
How often must I renew my participation in the TIRF REMS Access Program?
I do not have any specific questions. I have never dispensed any of these medications. Although I have reviewed the medication information through this program, I would like more information regarding the meds so that I can better undersatand them.
Some doctors are requesting higher doses than recommended as the patient builds tolerance. I assume the dosage limits are accurate in the prescribing information and have they changed?
what are the side effects of the meds
NO QUESTIONS
none that I can think of.
NO QUESTION..THOUGHT ASKING IF WE ANSWERED PATIENT'S QUESTION...MISUNDERSTOOD
N/A
no questions
No questions
WHY THESE PRODUCTS OVER OTHER ITEMS
I believe we had to call and obtain information about drug disposal.
None at this moment.
N/A
None

Appendix C Pharmacy Survey Protocol Track Change Document: Comparison of 24-month Survey to 36-month Survey

PROTOCOL TITLE:	**Quantitative Testing of Pharmacist Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)**
	Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)
	Depomed, Inc
	Galena Biopharma, Inc.
	Insys Therapeutics
	Mallinckrodt Pharmaceuticals
	Meda Pharmaceuticals
	Mylan, Inc.
	Par Pharmaceutical, Inc.
VERSION:	**6.0**
DATE:	**18MAY2014**
APPROVED:	**Final**

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Deleted: 10 Sep 2013

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TABLE OF CONTENTS **PAGE**

	TABLE OF CONTENTS	2
1.	LIST OF ABBREVIATIONS	3
2.	BACKGROUND	4
3.	OBJECTIVES OF THE EVALUATION SURVEY	5
4.	METHODS	5
4.1	Survey Design	5
4.1.1	Qualitative Research on the Survey	6
4.1.2	Questions and Statements on REMS Goals	6
4.1.3	Additional Questions	9
4.2	Participant Recruitment	10
4.2.1	Measures to Minimize Bias in the Sample	10
5.	STUDY POPULATION	10
5.1.1	Sample Size	10
5.1.2	Inclusion Criteria	11
5.1.3	Exclusion Criteria	11
6.	SURVEY PROCESS	12
6.1	Screening and Survey Administration	12
6.1.1	Telephone	12
6.1.2	Internet	12
6.2	Measures to Minimize Bias in the Survey Process	12
7.	ANALYSIS	13
7.1.1	Analysis Population	13
7.1.1.1	Description of Primary Analyses	13
7.1.1.2	Description of Secondary Analyses	14
8.	SAFETY EVENT REPORTING	14
9.	PRIVACY PROTECTION AND CONFIDENTIALITY	14

LIST OF APPENDICES

Appendix A	Pharmacist Questionnaire	15
Appendix B	SAMPLE Pharmacist Invitation Letter	33

1. LIST OF ABBREVIATIONS

CATI	Computer-Assisted Telephone Interviewing
CSP	Closed System Pharmacy
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ISI	Important Safety Information
KAB	Knowledge, Attitudes and Behavior
PI	Prescribing Information
REMS	Risk Evaluation and Mitigation Strategy
SE PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access Program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

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2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Meda Pharmaceuticals; Mallinckrodt Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients
2. Preventing inappropriate conversion between TIRF medicines
3. Preventing accidental exposure to children and others for whom it was not prescribed
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

An important component of the TIRF REMS is the conduct of quantitative evaluation surveys to assess pharmacists' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS educational materials, enrollment form, and Prescribing Information (PI). This protocol will describe the administration of the surveys that will be conducted among pharmacists who are enrolled in the TIRF REMS Access Program.

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

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The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

3. OBJECTIVES OF THE EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of pharmacists around the following key information and risk messages communicated through REMS:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.
2. TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 or older for Actiq® and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
3. TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.
4. TIRF medicines are not interchangeable with each other, regardless of route of administration.
5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey will also collect data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC), and will be administered by UBC.

4.1 Survey Design

This survey will be conducted among a sample of pharmacists who are enrolled in the TIRF REMS Access Program. Respondents who have participated in a previous wave of the TIRF survey will not be eligible to participate in subsequent survey waves.

The survey will be administered using the following modalities:

- Self-administered via the Internet through a secure website

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- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take up to 20 minutes.

The survey included in Appendix A is written to reflect wording for both methods of survey administration: Internet-based and telephone.

All respondents who complete the survey and who provide their contact information will be mailed a $50 honorarium for their time.

4.1.1 Qualitative Research on the Survey

The FDA provided feedback to the TRIG on the Knowledge, Attitude, and Behavior (KAB) survey results for pharmacists included in the 12-month REMS Assessment results. The FDA requested that the TRIG investigate the causes for low correct response rates to specific questions in the survey by conducting research to determine the reasons for the poor performance on these questions and to assess proposed revised wording to select questions. Qualitative research was performed in 2013 prior to Wave 2 of the survey. Findings were incorporated into the survey and results from the revised survey were included in the 24-month REMS Assessment Report.

4.1.2 Questions and Statements on REMS Goals

The KAB questionnaire is made up of multiple-choice, close-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and one open-ended question. These will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3.

Questions will be presented in several formats:

- Statements or questions asking the respondent to indicate whether a statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use "yes" or "no" as potential response options);
- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and
- One question allowing for the respondent to list questions or comments.

Questionnaires will be analyzed to determine pharmacist understanding of each key risk message.

For statements or questions that use "true" or "yes" vs. "false" or "no" response options, the desired response for the key risk messages is generally "true" or "yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions are

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Among the pharmacists interviewed, the most notable finding was that their survey responses should be based on ("according to") the TIRF medicines label The findings from this research have been incorporated into the survey in Appendix A The qualitative research report can be found in Appendix C ¶

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formatted to have the respondent disagree with the statement as written by providing response options of "false" or "no" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired response**
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a	Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	**TRUE**
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before	**FALSE**
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	**FALSE**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**TRUE**
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	**TRUE**
7c	TIRF medicines may be used in opioid non-tolerant patients.	**FALSE**
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	**TRUE**

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.		
Question No.	**Question**	**Desired response**
9	Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a	Acute or postoperative pain	**NO**
9b	Headache or migraine pain	**NO**
9c	Dental pain	**NO**
9d	Breakthrough pain from cancer	**YES**
9e	Chronic non-cancer pain	**NO**

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Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance with abuse liability similar to other opioid analgesics.		
Question No.	**Question**	**Desired response**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**TRUE**
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a	A personal history of psychiatric illness	**YES**
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**YES**
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10a	TIRF medicines can be abused in a manner similar to other opioid agonists.	**TRUE**

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired response**
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10b	TIRF medicines are interchangeable with each other regardless of route of administration.	**FALSE**
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	**TRUE**
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**TRUE**

4.1.3 Additional Questions

The survey includes questions about the requirements of the TIRF REMS Access Program, receipt and understanding of the TIRF educational materials, and behaviors. The following question about behaviors will be asked after the key risk message questions.

Question 12: How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.
Ask patients (or their caregivers) about the presence of children in the home
Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
Give patients (or their caregivers) the Medication Guide for their TIRF medicine

Demographic information will be collected at the end of the survey.

4.2 Participant Recruitment

A random sample of "pharmacists in charge" from pharmacies that are enrolled in the TIRF REMS Access Program will be invited to participate via an invitation letter. Any pharmacist who works at an enrolled pharmacy may participate. The text of the sample written invitation to pharmacists can be found in Appendix B.

If the required number of completed surveys is not achieved within the expected timeframe of approximately one to two weeks after the first mailing, reminder letters will be sent to non-responders from the original sample with subsequent fax, e-mail, or United States (US) Mail follow-up to maximize participation. The distribution within the mailing to the second sample will be adjusted in accordance with the allocation in the original sample. If these efforts do not result in the required number of surveys within two to three weeks, then a new sample of pharmacists will be randomly selected. The unique code provided in the invitation letter will be linked to the type of pharmacy (inpatient, outpatient, or Closed System Pharmacy [CSP]) in which the pharmacist works, based on the information provided as part of the TIRF REMS Access Program enrollment.

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All respondents who complete the survey and who provide their contact information will be mailed a $50 honorarium to thank them for their participation. The mailing will include a Thank You Letter, a copy of the Important Safety Information (ISI), and a copy of the correct answers to key risk message questions.

4.2.1 Measures to Minimize Bias in the Sample

The sample of participating pharmacists will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of pharmacies (e.g., chain and independent store) for participation.

Pharmacists will be offered Internet-based or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the Internet-based survey or when calling the Survey Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

5. STUDY POPULATION

5.1.1 Sample Size

A sample of 300 pharmacists who are enrolled in the TIRF REMS Access Program is proposed for each survey wave. The size of the sample was determined based on both practical and statistical considerations. There is no target comprehension rate specified *a priori*. A sample of 300 completed surveys will allow estimation of the comprehension rate

for each risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval	
5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.2 Inclusion Criteria

Pharmacists who work at pharmacies that are enrolled in the TIRF REMS Access Program are eligible to participate in this survey, with the exceptions noted below.

5.1.3 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Pharmacists who have previously participated in the TIRF REMS KAB survey.
- Pharmacists or their immediate family members who have ever worked for Anesta LLC; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc.; Par Pharmaceutical, Inc.; Teva Pharmaceuticals, Ltd.; UBC; McKesson Specialty Care Solutions; RelayHealth; or the FDA.

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6. SURVEY PROCESS

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm pharmacist eligibility. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, the respondent is immediately notified with a "thank you" message that survey participation has ended. If eligible, the respondent is allowed to continue survey participation.

The data entry system used for both methods of survey administration has been validated and is secure for receiving and storing survey data. An Internet-based data repository will be used to store survey data and other relevant program information. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Pharmacist-identifying information will be stored separately from survey data.

6.1.1 Telephone

A trained interviewer from the Survey Coordinating Center will conduct the telephone interviews using a CATI program. The screening and main elements of the questionnaire will be administered sequentially during the same telephone call.

Telephone interviewing allows participation of pharmacists who do not have Internet access or prefer taking the survey over the telephone. It will also be convenient for pharmacists to participate since they can call in and be interviewed at their convenience during the specified time period when the Survey Coordinating Center is available.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If the pharmacist selects to participate in the survey via the Internet, he/she will be directed to a secured website where he/she will be instructed to complete screening questions. An Internet-based survey will be convenient for respondents to participate since they can complete the questionnaire at any convenient time and location during the specified time period when the Survey Coordinating Center is available.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer the survey.

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All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question

once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. The data from the sample population will be reported using frequency distributions of responses to all questions.

The following will be reported as part of this analysis:

- The number of invitations issued to pharmacists
- The number of reminder letters issued to pharmacists
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents eligible for participation who answered all questions presented to them
- Representativeness of pharmacists based on geography
- Description of survey participants, including:
    - Gender
    - Years of professional experience
    - How many times per month TIRF medicines dispensed in the last 6 months

Additional descriptive statistics may be reported as appropriate.

7.1.1 Analysis Population

The analysis population will be based on eligible pharmacists who completed all questions presented to them in the survey ("completers").

7.1.1.1 Description of Primary Analyses

Primary analyses are done for all key risk messages using data from all completers. The primary analysis for a key risk message evaluates the rate for each correct response to each individual question/item defined by the key risk message. The specific correct response to each question/item is identified in the body of the risk message table.

7.1.1.2 Description of Secondary Analyses

Secondary analyses are done only for those key risk messages that contain multiple questions/items using data from all completers. The secondary analysis entails a frequency distribution of the number of completers who got 0, 1, etc. correct responses across the total number of items for the given key risk message.

8. SAFETY EVENT REPORTING

The term 'Safety Event' is defined as any information reported by a survey respondent that meets the criteria of an adverse event or product complaint. While it is not the intention of the survey to solicit the report of information that meets the criteria of a Safety Event, it is possible that a respondent may spontaneously report information that meets this criteria in free text fields of the survey (Internet-based administration) or while in conversation with the Survey Coordinating Center (telephone-based administration). The Internet-based questionnaires will be monitored for any comments recorded in the free text fields. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. Respondents will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact them if they have questions about the survey. Information on all reports (Internet or telephone) that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE PSP.

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9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The electronic data capture (EDC) system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail the $50 honorarium, a Thank You Letter, correct survey responses to key risk message questions, and the ISI after the survey is completed. Respondent contact information is also needed in the event that a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information (see Section 8 above).

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to dispense TIRF medicines.

Appendix A Pharmacist Questionnaire

Survey Legend

- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.

- **(INTERVIEWER)** is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by telephone only (for example, spontaneous adverse event reporting).

- **[ONLINE]** indicates a question is worded specifically for administering the survey online. **[PHONE]** indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.

- **[BEGIN ONLINE/PHONE SURVEY CONTENT]** and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.

- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

  Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.

- **[RANDOMIZE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as "I don't know," "Prefer not to answer" or "None of the above" will always appear at the end of the randomized responses.

- **[GO TO Qx]** (skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

- **[FREE TEXT]** indicates to the programmer that one line should be provided for data entry.

- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be

provided for data entry (for example, two address lines)

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- **[DROP-DOWN LIST INPUT WITH STATES TABLE]** indicates to the programmer that the response should be a drop-down list containing the states in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

Northeast Region

- New England Division - ME, NH, VT, MA, RI, CT
- Middle Atlantic Division - NY, NJ, PA

Midwest Region

- East North Central Division - OH, IN, IL, MI, WI
- West North Central Division - MN, IA, MO, ND, SD, NE, KS

South Region

- South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
- East South Central Division - KY, TN, AL, MS
  West South Central Division - AR, LA, OK, TX

West

Survey Legend

- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV
- Pacific Division WA, OR, CA, AK, HI

The following US territories are categorized as Other: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

[BEGIN SURVEY CONTENT]

[ONLINE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess pharmacists' understanding of the safe use and dispensing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc. The survey will take 15-20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to dispense TIRF medicines.

How We Use Your Information

Your answers to the survey questions will be combined with answers given by other pharmacists taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 honorarium for your time and participation.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

How to Learn More about This Survey

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If you have questions about the survey, or problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Be sure to write down this telephone number; it will not be displayed again.

Taking the Survey

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

[PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess pharmacists' understanding of the safe use and dispensing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." **(INTERVIEWER: Say "TIRF" then spell out T-I-R-F)** The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc. The survey will take 15-20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to dispense TIRF medicines.

Now I would like to read some information about how your contact information will be used.

Your answers to the survey questions will be combined with answers given by other pharmacists taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 honorarium for your time and participation.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

Now I would like to tell you some information about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

Now I will tell you how you can learn more about this survey. Please have a pen or pencil ready to write down a telephone number you can call should you have any questions about the survey. If you have questions about the survey, please ask me at any time. If you have questions at a later time, please contact the Survey Coordinating Center at 1-877-379-3297.

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Please feel free to ask me to repeat any questions or statements as we go through the survey. Once you have answered a question and moved on, you cannot go back and change your answers. Thank you for your participation in this survey.

[END PHONE PREAMBLE 1]

[BEGIN INCLUSION/EXCLUSION QUESTIONS]

1. Your agreement to participate in this survey confirms mutual understanding in connection with completion of the survey and the fair market value of the payment to be rendered in connection with those services.

   Do you agree to participate in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

   - ○ Yes **[TERMINATE]**
   - ○ No
   - ○ I don't know **[TERMINATE]**

3. Do you work in a pharmacy that is enrolled in the TIRF REMS Access Program?

   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

4. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

   - □ Anesta LLC **[TERMINATE]**
   - □ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**
   - □ Depomed, Inc. **[TERMINATE]**
   - □ Galena Biopharma, Inc. **[TERMINATE]**
   - □ Insys Therapeutics **[TERMINATE]**

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- ☐ Mallinckrodt Pharmaceuticals **[TERMINATE]**
- ☐ McKesson Specialty Care Solutions **[TERMINATE]**
- ☐ Meda Pharmaceuticals **[TERMINATE]**
- ☐ Mylan, Inc. **[TERMINATE]**
- ☐ Par Pharmaceutical, Inc. **[TERMINATE]**
- ☐ RelayHealth **[TERMINATE]**
- ☐ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- ☐ United BioSource Corporation **[TERMINATE]**
- ☐ FDA **[TERMINATE]**
- ☐ None of these apply **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- ☐ I don't know **[TERMINATE]**
- ☐ Prefer not to answer **[TERMINATE]**

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[END INCLUSION/EXCLUSION QUESTIONS]

5. Please select True, False, or I don't know for each of the following.

According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
5a.	Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	○	○	○
5b.	Who are not currently taking opioid therapy, but have taken opioid therapy before	○	○	○
5c.	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	○	○	○

6. Please answer True, False, or I don't know for each statement based on the labeling for

TIRF medicines.

[RANDOMIZE LIST]	True	False	I don't know
6a. A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time.	○	○	○
6b. A cancer patient who has been on an around-the-clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.	○	○	○

7. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

[RANDOMIZE LIST]	True	False	I don't know
7a. TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	○	○	○
7b. Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	○	○	○
7c. TIRF medicines may be used in opioid non-tolerant patients.	○	○	○
7d. Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	○	○	○
7e. It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	○	○	○

8. Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
8a.	A personal history of psychiatric illness	○	○	○
8b.	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	○	○	○
8c.	A family history of asthma	○	○	○

9. Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
9a.	Acute or postoperative pain	○	○	○
9b.	Headache or migraine pain	○	○	○
9c.	Dental pain	○	○	○
9d.	Breakthrough pain from cancer	○	○	○
9e.	Chronic non-cancer pain	○	○	○

10. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
10a.	TIRF medicines can be abused in a manner similar to other opioid agonists.	○	○	○
10b.	TIRF medicines are interchangeable with each other regardless of route of administration.	○	○	○
10c.	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	○	○	○
10d.	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	○	○	○

11. Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:

[RANDOMIZE LIST]	True	False	I don't know
11a. 8 mg oral hydromorphone/day	○	○	○
11b. 60 mg oral morphine/day	○	○	○
11c. 30 mg oral oxycodone/day	○	○	○
11d. 25 mcg transdermal fentanyl/hour	○	○	○
11e. 25 mg oral oxymorphone/day	○	○	○
11f. An equianalgesic dose of another oral opioid	○	○	○

12. How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.

[RANDOMIZE LIST]	Always	Only with the first prescription	Sometimes	Never	I don't know
12a Ask patients (or their caregivers) about the presence of children in the home	○	○	○	○	○
12b Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	○	○	○	○	○
12c Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	○	○	○	○	○
12d Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	○	○	○	○	○
12e Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	○	○	○	○	○
12f. Give patients (or their caregivers) the Medication Guide for their TIRF medicine	○	○	○	○	○

13. Please answer True, False, or I don't know for each statement about TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
13a.	TIRF medicines may be sold, loaned, or transferred to another pharmacy.	○	○	○
13b.	All pharmacy staff that dispenses TIRF medicines must be educated on the requirements of the TIRF REMS Access Program.	○	○	○
13c.	TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.	○	○	○

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14. [INPATIENT PHARMACIST] Does the inpatient pharmacy where you work have an established system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access Program?

- ○ Yes
- ○ No
- ○ I don't know

15. [OUTPATIENT PHARMACIST] Does the outpatient or retail pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the pharmacy management system?

- ○ Yes
- ○ No
- ○ I don't know

16. **[CSP OUTPATIENT PHARMACIST]** Does the pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the TIRF REMS Access Call Center?

- ○ Yes
- ○ No
- ○ I don't know

17. **[INPATIENT PHARMACIST]** Please answer True, False, or I don't know for the following statement about TIRF medicines.

	True	False	I don't know
It is OK to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for use at home.	○	○	○

[PREAMBLE 3]

The next set of questions is about the educational materials for TIRF medicines. As a reminder, the TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

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18. Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No **[GO TO Q20]**
- ○ I don't know **[GO TO Q20]**

19. Did you read the Full Prescribing Information for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No
- ○ I don't know

20. Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No **[GO TO Q22]**
- ○ I don't know **[GO TO Q22]**

21. Did you read the Medication Guide for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No
- ○ I don't know

22. Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?

- ○ Yes
- ○ No **[GO TO DEMOGRAPHICS PREAMBLE]**
- ○ I don't know **[GO TO DEMOGRAPHICS PREAMBLE]**

23. What are your questions? **[MULTILINE INPUT]**

[DEMOGRAPHICS PREAMBLE]

There are just a few more questions to help us combine your answers with other answers we have received.

24. Are you the Pharmacist in Charge for the TIRF REMS Access Program where you work?

- ○ Yes
- ○ No
- ○ I don't know

25. On average, how many times per month have you dispensed TIRF medicine within the last 6 months?

- ○ None **[Go to DEMOGRAPHICS PREAMBLE 2]**
- ○ 1 – 2 times per month
- ○ 3 – 5 times per month
- ○ More than 5 times per month
- ○ I don't remember

26. Please select the TIRF medicine(s) that you have dispensed within the last 6 months. Please select all that apply.

- ☐ Abstral®
- ☐ Actiq® or generic Actiq®
- ☐ Fentora®
- ☐ Lazanda®
- ☐ Onsolis®
- ☐ Subsys®

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[DEMOGRAPHICS PREAMBLE 2]

These last few questions are for demographic purposes.

27. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

28. In total, how many years have you been a practicing pharmacist?

- ○ Less than 3 years
- ○ 3 – 5 years
- ○ 6 – 10 years
- ○ 11 – 15 years
- ○ More than 15 years
- ○ Prefer not to answer

29. In which state do you practice?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" AT END]

[PHONE ONLY: BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- ○ Yes
- ○ No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[CLOSING 1]

We would like to send you a $50 honorarium within the next few weeks to thank you for your time, but we need your name and address to do so. If you do not provide your name and address you will not receive the honorarium for your time and participation in the survey.

Do you agree to give us your name and mailing address so we can send you the honorarium?

- Yes
- No **[SKIP TO CLOSING 2]**

FIRST NAME: **[FREE TEXT]**

LAST NAME: **[FREE TEXT]**

ADDRESS: **[MULTILINE INPUT]**

CITY: **[FREE TEXT]**

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: **[5 NUMERIC CHARACTERS ONLY]**

[CLOSING 2]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

Do you want to provide your telephone number?

- Yes
- No **[SKIP TO CLOSING 3]**

Telephone: **[MUST BE 10-DIGIT NUMERIC CHARACTERS]**

[END CLOSING 2]

[CLOSING 3]

That ends the survey. Thank you again for your help.

[END OF SURVEY CONTENT]

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Appendix B SAMPLE Pharmacist Invitation Letter

[CURR_DATE]

[PHARMACY_NAME]

[PHARMACY _STREET_ADDR]
[PHARMACY_CITY], [PHARMACY _STATE] [PHARMACY _ZIP]

[PHARMACY_FAX_NUMBER]

Dear [PHARMACIST_IN CHARGE]

Your Pharmacy was selected to receive this letter, because of enrollment in the TIRF REMS Access Program. We are contacting you to inform you about a survey being conducted by the manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines, as required by the Food and Drug Administration (FDA). The purpose of the survey is to assess pharmacists' understanding of the safe and appropriate use of these medicines. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

The manufacturers of TIRF medicines include Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Meda Pharmaceuticals; Mallinckrodt Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc. (collectively referred to as the "TIRF REMS Industry Group"). These manufacturers are looking for 300 pharmacists to complete the survey. Eligible pharmacists who complete the survey will be sent a $50 honorarium to thank them for their time. The survey will take 15-20 minutes.

Your answers will be kept strictly confidential and will be combined with the answers from other pharmacists who take this survey. Your name will not be used in the report of this survey and your contact information, if provided, will only be used to send you a $50 honorarium for your time to complete the survey.

You are under no obligation to participate in this survey. Only one pharmacist from each enrolled pharmacy can participate. If you are interested in participating and to find out if you are eligible:

- Go to www.TIRFREMSsurvey.com any time or
- Call 1-877-379-3297, 8 a.m. to 8 p.m. Eastern Time, Monday through Friday

Please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**. ***We recommend that you take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.***

Neither taking the survey nor your answers to the questions will affect your ability to dispense any of the TIRF medicines identified above.

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Sincerely,

The TIRF REMS Survey Team

1-877-379-3297

www.TIRFREMSsurvey.com

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Appendix C . Qualitative Research Report¶

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12.4.3 Prescriber KAB Survey

Title:	**Transmucosal Immediate Release Fentanyl (TIRF) REMS Assessment** **Quantitative Testing of Prescriber Knowledge, Attitudes, and Behavior (KAB) about TIRF Products' Safety and Use Information**
Document Number	Wave 3, 36-month REMS Assessment Version 1.0
Survey Time Period	18 August 2014 to 22 October 2014
Product Name:	Transmucosal Immediate Release Fentanyl
Sponsor:	**TIRF REMS Industry Group (TRIG) of Companies**: Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc. Galena Biopharma, Inc. Insys Therapeutics Mallinckrodt Pharmaceuticals Meda Pharmaceuticals Mylan, Inc. Par Pharmaceutical, Inc.
Date:	19 December 2014

Confidentiality Statement

TABLE OF CONTENTS **PAGE**

TABLE OF CONTENTS 2
LIST OF IN-TEXT TABLES 3
LIST OF APPENDICES 4
LIST OF ABBREVIATIONS 5
1. PRESCRIBER SURVEY BACKGROUND 6
2. PRESCRIBER SURVEY OBJECTIVES 7
3. SURVEY METHODOLOGY 7
3.1 Survey Sample 7
3.1.1 Eligibility 8
3.1.2 Recruitment 8
3.2 Questions and Statements on Key Risk Messages 8
3.2.1 Key Risk Message 1 9
3.2.2 Key Risk Message 2 10
3.2.3 Key Risk Message 3 11
3.2.4 Key Risk Message 4 12
3.3 Additional Questions 13
4. STATISTICAL METHODS 13
4.1 Study Population 13
4.1.1 Primary Analysis Population 13
4.1.2 Sub-groups of Interest 13
4.1.2.1 Primary Analyses 15
4.1.2.2 Secondary Analyses 15
4.1.3 Prescriber Report of an Adverse Event, Product Complaint, or Medical Information Request during the Survey 15
5. RESULTS 15
5.1 Survey Participants 16
5.1.1 Survey Participant Administration Results 16
5.1.2 Description of Eligible Prescribers who Completed the Survey 19
5.1.3 TIRF Medicines Educational Materials 22

5.2 KAB Survey Objectives 24
5.2.1 Key Risk Message Results 24
5.2.1.1 Key Risk Message 1 25
5.2.1.2 Key Risk Message 2 27
5.2.1.3 Key Risk Message 3 30
5.2.1.4 Key Risk Message 4 32
5.2.2 Other Survey Questions 34
5.2.2.1 Additional Questions about TIRF Medicines Safety 34
5.2.2.2 Prescriber Activities When Prescribing TIRF Medicines 40
5.2.3 Sub-group Analysis of Responses to Key Risk Messages 42
5.3 Spontaneous Reporting of Adverse Events, Product Complaints or Medical Information Requests 43
5.4 Summary of Correct Responses for Key Risk Messages 44
6. FDA FEEDBACK 48
7. DISCUSSION AND CONCLUSIONS 48

LIST OF IN-TEXT TABLES

Table 1. Survey Participant Administration Results 16
Table 2. Survey Participant Screening Results 17
Table 3. Time to Complete Survey for Completers Only 19
Table 4. Description of Eligible Prescribers 20
Table 5. Responses to Questions About the TIRF Medicines Educational Materials and the TIRF Patient-Prescriber-Agreement Form 23
Table 6. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients 25
Table 7. Responses Linked to Key Risk Message 2: TIRF Medicines Are Only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (16 Years of Age and Older for Actiq® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain 28
Table 8. Responses Linked to Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist, and a Schedule II Controlled Substance, With Abuse Liability Similar to Other Opioid Analgesics 31

Table 9. Responses Linked to Key Risk Message 4: TIRF Medicines Are Not Interchangeable With Each Other, Regardless of Route of Administration. 33
Table 10. Responses to Additional Questions About the Safe Use of TIRF Medicines 36
Table 11. Responses to All Questions About Activities When Prescribing TIRF Medicines 41
Table 12. Percentage of All Correct Responses to Key Risk Messages based on Sub-Groups 1 and 5 - Sub-Group Analysis 1: Reading Medication Guide or full Prescribing Information - Sub-Group Analysis 5: Modality to Complete Survey 43
Table 13. Summary of Correct Responses for Key Risk Messages 45
Table 14. Desired Response of Low Scoring Questions Across the Three Prescriber KAB Survey Waves 50

LIST OF APPENDICES

Appendix A Prescriber Survey Protocol 52
Appendix B Prescriber Survey Listings and Sub-group Analysis Tables 53
Appendix C Prescriber Survey Protocol Track Change Document: Comparison of 24-month Survey to 36-month Survey 54

LIST OF ABBREVIATIONS

AE/PC PSP	Adverse Event/Product Complaint Project Specific Procedure
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
KAB	Knowledge, Attitudes, and Behavior
MA	Massachusetts
MN	Minnesota
NA	Not Applicable
PPAF	Patient-Prescriber Agreement Form
REMS	Risk Evaluation and Mitigation Strategy
SD	Standard Deviation
SCC	Survey Coordinating Center
TIRF	Transmucosal Immediate Release Fentanyl
TIRF medicines	Transmucosal Immediate Release Fentanyl product(s)
TIRF REMS Access Program	REMS Program for TIRF medicines
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States
USPS	United States Postal Service
VT	Vermont

1. PRESCRIBER SURVEY BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines are a class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® [fentanyl citrate oral transmucosal lozenge] and equivalent generics) who are receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and their generic equivalents. The TIRF Risk Evaluation and Mitigation Strategy (REMS) Industry Group (TRIG) includes Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.), Depomed, Inc., Galena Biopharma, Inc., Insys Therapeutics, Mallinckrodt Pharmaceuticals, Meda Pharmaceuticals, Mylan, Inc., and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a shared system REMS is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on 28 December 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by the following:

- Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
- Preventing inappropriate conversion between TIRF medicines.
- Preventing accidental exposure to children and others for whom it was not prescribed.
- Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess prescribers' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS educational materials, enrollment form, and Prescribing Information of each product. Administration of the surveys conducted among prescribers who are enrolled in the TIRF REMS Access Program is described in the protocol (See Appendix A). Note: Protocol and Survey question revisions are identified in the track change version found in Appendix C.

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

This report describes the results from the prescriber survey conducted for the 36-month TIRF REMS Access Program Assessment. The 36-month prescriber knowledge, attitudes, and behavior (KAB) survey launched on 18 August 2014 and closed on 22 October 2014.

2. PRESCRIBER SURVEY OBJECTIVES

The evaluation survey uses a questionnaire to document the level of knowledge and assess the attitudes and behaviors of prescribers regarding the following key information and risk messages communicated through the REMS:

- TIRF medicines are contraindicated in opioid non-tolerant patients.
- TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 or older for Actiq® and equivalent generics) who are receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
- TIRF medicines contain fentanyl, an opioid agonist, and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.
- TIRF medicines are not interchangeable with each other, regardless of route of administration.
- Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey also collects data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

3. SURVEY METHODOLOGY

This section summarizes the survey design and the questions that were constructed to test prescriber understanding of the key risk messages of the REMS. Full details of the survey design are in the protocol, which can be found in Appendix A.

3.1 Survey Sample

This survey was conducted among a random sample of prescribers who were enrolled in the TIRF REMS Access Program as of 05 August 2014. A target sample of 300 prescribers who were enrolled in the TIRF REMS Access Program was surveyed in this third KAB survey conducted from 18 August 2014 to 22 October 2014. The size of the sample was determined on both practical and statistical considerations. The survey was written to reflect wording for both methods of survey administration: Internet-based and telephone.

3.1.1 Eligibility

Subjects were recruited from a random sample of prescribers who were enrolled in the TIRF REMS Access Program. Respondents or respondents with immediate family members who had ever worked for any of the TRIG companies, RelayHealth, McKesson Specialty Care Solutions, United BioSource Corporation (UBC), or the FDA were not eligible to participate.

Respondents who participated in the previous waves of the survey (12-month TIRF REMS Access Program Assessment or the 24-month TIRF REMS Access Program Assessment) were not eligible to participate.

3.1.2 Recruitment

Subjects were recruited via an invitation letter sent through the United States Postal Service (USPS), or via email (Section 5.1.1 for more detail).

The required number of completed surveys was not achieved within approximately 10 days after the first mailing; thus, additional mailings were distributed to non-respondents from the original sample to maximize participation.

Each letter of invitation included a unique code needed to complete the survey. Prescribers were given the option of taking the survey by telephone via the Survey Coordinating Center (SCC) or online via a secure website. All participating prescribers were offered an honorarium of $125 for a completed survey. The survey was estimated to take approximately 20 minutes to complete.

3.2 Questions and Statements on Key Risk Messages

The questions and statements comprising the knowledge survey were constructed to test the prescribers' understanding of the key risk messages of the REMS. The questions were to be answered either by selecting options from multiple-choice lists that include statements of the specific key risk messages or by choosing "Yes" or "True," "No" or "False," or "I Don't Know" regarding statements about TIRF medicines.

For statements or questions that use "True" or "Yes" vs. "False" or "No" response options, the desired response for key risk messages is generally "True" or "Yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions were formatted to have the respondent disagree with the statement as written by providing response options of "False" or "No" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

3.2.1 Key Risk Message 1

Key Risk Message 1 referred to the prescriber's knowledge of TIRF medicine contraindication in opioid non-tolerant patients.

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired response**
5	**Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:**	
5a	Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer	***True***
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before	***False***
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	***False***
7	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	***True***
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	***True***
7c	TIRF medicines may be used to treat opioid non-tolerant patients.	***False***
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	***True***

3.2.2 Key Risk Message 2

Key Risk Message 2 referred to the prescriber's knowledge of the indications for prescribing TIRF medicines for the management of breakthrough pain in opioid-tolerant adult cancer patients. This key risk message includes both a behavior question (Question 9) and a knowledge question (Question 13).

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.		
Question No.	**Question**	**Desired response**
9	In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.	
9a	Acute or postoperative pain	***No***
9b	Headache or migraine pain	***No***
9c	Dental pain	***No***
9d	Breakthrough pain from cancer	***Yes***
9e	Chronic non-cancer pain	***No***
13	The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.	***13b. Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.***

3.2.3 Key Risk Message 3

Key Risk Message 3 referred to the prescriber's knowledge of the risk factors and signs and symptoms of opioid abuse in patients who take TIRF medicines.

Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II-controlled substance, with abuse liability similar to other opioid analgesics.		
Question No.	**Question**	**Desired response**
7	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	***True***
8	Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.	
8a	A personal history of psychiatric illness	***Yes***
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	***Yes***
10	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
10a	TIRF medicines can be abused in a manner similar to other opioid agonists.	***True***

3.2.4 Key Risk Message 4

Key Risk Message 4 referred to the prescriber's knowledge of the interchangeability of TIRF medicines based on route of administration, pharmacokinetic absorption, and dosage.

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired response**
10	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
10b	TIRF medicines are interchangeable with each other regardless of route of administration.	***False***
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	***True***
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	***True***
14	A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.	***14b. The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.***

3.3 Additional Questions

The survey also contained questions (Question 12a-f) about the requirements of the TIRF REMS Access Program and the use of the TIRF educational materials in their practice. The following questions about behaviors were asked after the key risk message questions:

Question No.	Question
12	How frequently do you perform the following activities when dispensing TIRF medicines? Please answer "Always," "Only with the first prescription," "Sometimes," "Never," or "I don't know."
12a	Ask patients (or their caregivers) about the presence of children in the home
12b	Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
12c	Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
12d	Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
12e	Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
12f	Give patients (or their caregivers) the Medication Guide for their TIRF medicine

4. STATISTICAL METHODS

4.1 Study Population

4.1.1 Primary Analysis Population

The primary population for analysis was all eligible prescribers who completed the survey. Eligible prescribers were defined as those respondents who answered ***Yes*** to Question 1 (agree to take part in survey) and to Question 3 (enrolled in the TIRF REMS Access program), and ***No*** to Question 2 (participated in past survey) and to Question 4 (worked for a TRIG company, UBC, RelayHealth, McKesson Specialty Care Solutions, or FDA). A completed survey was a survey from an eligible prescriber in which all non-eligibility questions were answered as appropriate. Note that some questions may not be answered because of skip logic in the survey questionnaire.

4.1.2 Sub-groups of Interest

The following sub-group analyses of responses to key risk messages were conducted when the sub-group included at least 20 respondents. Of note, sub-group analysis 4 was not done since only 18 prescribers completed the survey via telephone.

Sub-group analysis 1: Reading Medication Guide or Full Prescribing Information (Questions 20, 21, 22, and 23):

- S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.
- S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 23).

Sub-group analysis 2: Medical degree of respondents (Question 32):

- S-2a - MD
- S-2b - DO
- S-2c - Nurse Practitioner
- S-2d - Physician Assistant

Sub-group analysis 3: Time to complete survey - Internet:

- S-3a - <10 min
- S-3b - 10 to <20 min
- S-3c - ≥ 20 min

Sub-group analysis 4: Time to complete survey - Telephone:

- S-4a - <10 min
- S-4b - 10 to <20 min
- S-4c - ≥ 20 min

Sub-group analysis 5: Modality to complete survey:

- S-5a - Internet
- S-5b – Telephone

Sub-group analysis 6: Time practicing medicine (Question 33):

- S-6a - Less than 3 years
- S-6b - 3 to 5 years
- S-6c - 6 to 15 years
- S-6d - More than 15 years

Sub-group analysis 7: Number of times per months prescribing TIRF medicines within the last 6 months (Question 29):

- S-7a - None
- S-7b - 1-2 times a month
- S-7c - 3 - 5 times a month
- S-7d - More than 5 times a month

Results of sub-group analyses performed are provided in Appendix B.

4.1.2.1 Primary Analyses

Primary analyses were performed for all key risk messages, evaluating the number and percentage of correct responses for each individual question/item defined by the key risk message. The correct response to each question/item was identified in the body of the risk message table (Section 3.2).

4.1.2.2 Secondary Analyses

Secondary analyses evaluated the number and percentages of correct responses and the average number of correct answers within the risk message to assess demonstrated understanding of the comprehensive key risk message. A correct response rate of 65% or greater was considered to represent adequate understanding of each concept or key risk message.

4.1.3 Prescriber Report of an Adverse Event, Product Complaint, or Medical Information Request during the Survey

A prescriber may have reported a product complaint, or an adverse event experienced by his/her patients either while taking the online survey in the free text field or while in conversation with the SCC Associate. If an event was mentioned to the SCC Associate, the Associate documented the safety event and the respondent's contact information, if provided. The prescriber was also informed that a representative from the appropriate TIRF medicine sponsor might contact him/her to obtain additional information about the adverse event or product complaint. Surveys completed on the Internet were monitored for any comments recorded in the free text field. Information on all reports (Internet or Telephone) that constituted an adverse event or product complaint was forwarded to the appropriate TIRF medicine sponsor for processing within 1 business day of awareness of the event as outlined in the Adverse Event/Product Complaint Project Specific Procedure (AE/PC PSP).

5. RESULTS

Results of the prescriber responses to questions in the KAB survey are summarized in this section, and a full set of responses can be found in Appendix B.

5.1 Survey Participants

5.1.1 Survey Participant Administration Results

A total of 4,499 prescribers were sent letters inviting them to participate in this survey (Table 1). An additional 12,526 reminder letters were sent in three separate mailings. Most prescribers may have received more than 1 reminder letter. There were no duplicate surveys. Note: Once the target number of 300 completed surveys was achieved, the survey was closed.

In all, 469 prescribers who expressed interest in the survey were screened for eligibility. The number of respondents found eligible for participating in the survey was 300 (64.0%), all of whom completed the survey – 282 (94.0%) completed the survey online, and 18 (6.0%) completed it by telephone (Table 1).

Based on the TRIG Sponsors interpretation of state laws regarding prescriber reimbursement, respondents from Massachusetts (MA), Vermont (VT), and Minnesota (MN) were eligible to participate in the survey; however, they were not eligible to receive the $125 honorarium. Invitation letters were sent to prescribers in these states, and 2 respondents from Massachusetts chose to participate despite receiving no honorarium.

Table 1. Survey Participant Administration Results

Summary Statistics	Screened Prescribers N=469[1]	
	All Respondents	
	N	%
Number of invitations issued to prescribers	4499	
Number of reminder letters issued to prescribers	12526	
Number of prescribers screened for participation	469[1]	
Number of prescribers eligible for participation	300[2]	64.0
Number of eligible prescribers who answered all questions presented to them	300	100.0
Methods of Survey Completion		
Number of surveys completed on telephone	18	6.0[3]
Number of surveys completed by Internet	282	94.0[3]

[1] The denominator for the percentage of eligible prescribers is the number of screened prescribers (N=469).
[2] The denominator for percentages of eligible prescribers completing the survey is the number of eligible prescribers. (N=300).
[3] The denominator for percentages completed by telephone or Internet is the number of eligible prescribers who completed the survey. (N=300).

As shown in Table 2, a total of 469 prescribers agreed to participate in this survey. During the screening process it was determined 169 respondents (36.0%) were not eligible to participate in the survey because they either indicated they had participated in or did not know whether they participated in a survey about TIRF medicines before, were not enrolled or did not know whether they were enrolled in the TIRF REMS Access Program, or indicated they, or an immediate family member, had worked for a TRIG company, UBC, or FDA in the past or did not know if they or an immediate family member had worked for a TRIG company, UBC, or FDA in the past. Thus, there were 300 eligible participants, all of whom completed the survey (Table 2).

Table 2. Survey Participant Screening Results

Question	All Respondents N=469		Eligible and Complete Respondents N=300	
	N	%	N	%
Question 1: Do you agree to participate in this survey?				
Yes	469	100.0	300	100.0
No [1]	0	0.0		
Question 2: Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.				
Yes [1]	44	9.4		
No	353	75.3	300	100.0
I don't know [1]	72	15.4		
Question not asked [2]	0	0.0		
Question 3: Are you enrolled in the TIRF REMS Access Program?				
Yes	313	66.7	300	100.0
No [1]	17	3.6		
I don't know [1]	23	4.9		
Question not asked [2]	116	24.7		

Table 2. Survey Participant Screening Results

Question	All Respondents N=469		Eligible and Complete Respondents N=300	
	N	%	N	%
Question 4: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply. [3]				
Anesta LLC. [1]	0	0.0		
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) [1]	2	0.4		
Depomed, Inc. [1]	1	0.2		
Galena Biopharma, Inc. [1]	2	0.4		
Insys Therapeutics [1]	5	1.1		
Mallinckrodt Pharmaceuticals [1]	1	0.2		
McKesson Specialty Care Solutions [1]	0	0.0		
Meda Pharmaceuticals [1]	0	0.0		
Mylan, Inc. [1]	1	0.2		
Par Pharmaceutical, Inc. [1]	0	0.0		
RelayHealth [1]	0	0.0		
Teva Pharmaceuticals, Ltd. [1]	1	0.2		
United BioSource Corporation [1]	0	0.0		
FDA[1]	2	0.4		
None of these apply [4]	300	64.0	300	100.0
I don't know [1]	4	0.9		
Prefer not to answer [1]	1	0.2		
Question not asked [2]	156	33.3		

[1] Ineligible to participate in the survey.

[2] Question not asked due to previous question elimination.

[3] More than one response can be selected, so percentages may not sum to 100%.

[4] Ineligible if selected in addition to another response.

Prescribers taking the online survey required a mean of 16.1 ± 7.81 minutes to complete the survey; prescribers taking it by telephone took a mean of 23.3 ± 3.23 minutes (Table 3).

Table 3. Time to Complete Survey for Completers Only

Time to Complete Survey (Minutes)			
Summary Statistic	**Telephone**	**Internet**	**Total[1]**
N	18	282	300
Mean (± SD)	23.3 ± 3.23	16.1 ± 7.81	16.5 ± 7.81
Minimum	19	6	6
Median	23.1	14.2	14.5
Maximum	32	57	57
Category			
0 to <5 Minutes	0	0	0
5 – <10 Minutes	0	50	50
10 – <15 Minutes	0	109	109
15 – <20 Minutes	3	64	67
20 – <25 Minutes	12	31	43
25 – <30 Minutes	2	10	12
30 Minutes or More	1	18	19

[1] Number of eligible prescribers completing the survey (See Table 1).

SD = Standard Deviation

5.1.2 Description of Eligible Prescribers who Completed the Survey

The demographic characteristics of prescribers who completed the survey are shown in Table 4.

On average within the preceding 6 months, 154 (51.3%) prescribers had prescribed a TIRF medicine 1-2 times per month; 26 had prescribed more than 5 times per month, while 64 (21.3%) had not prescribed any TIRF medicine.

The most common healthcare degree was an MD (62.0%), and the most common medical specialties were pain management (50.7%) and oncology (24.0%). The present survey included 123 (41.0%) respondents who had practiced medicine for more than 15 years; 110 (36.7%) for 6-15 years; 30 (10.0%) were in practice for less than 3 years and 35 (11.7%) for 3-5 years. The most frequently prescribed TIRF medicine within the last 6 months prior to taking the survey was Actiq® or generic Actiq® (162 prescribers, 68.6%). Note: Ten prescribers indicated that they prescribed Onsolis® during the 6 months prior to taking the

survey. However, Onsolis® was not available at that time. Onsolis® was last available in May 2011.

The survey included 25.3% respondents from the Northeast, 14.7% from the Midwest, 32.0% from the South, and 27.7% from the West region of the United States (US). There were no respondents from Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam identified as "Other" in Table 4.

Table 4. Description of Eligible Prescribers

Question	Eligible Completed Prescribers N=300[3]	
	n	%
Question 29: On average, how many times per month have you prescribed the TIRF medicines within the last 6 months?		
None	64	21.3
1 – 2 times per month	154	51.3
3 – 5 times per month	45	15.0
More than 5 times per month	26	8.7
I don't remember	11	3.7
Question 30: Please select the TIRF medicines that you have prescribed within the last 6 months. Please select all that apply.		
Abstral®	31	13.1
Actiq ® or generic Actiq®	162	68.6
Fentora ®	140	59.3
Lazanda ®	25	10.6
Onsolis ®	10	4.2
Subsys ®	80	33.9
N/A (answered ***None*** to Question 29)	64	
Question 31: What is your gender?		
Male	178	59.3
Female	111	37.0
Prefer not to answer	11	3.7

Table 4. Description of Eligible Prescribers

Question	Eligible Completed Prescribers N=300[3]	
	n	%
Question 32: What is your medical degree?		
MD	186	62.0
DO	23	7.7
Nurse Practitioner	53	17.7
Physician Assistant	36	12.0
Prefer not to answer	2	0.7
Question 33: In total, how many years have you been practicing medicine, since completing your post-graduate education?		
Less than 3 years	30	10.0
3-5 years	35	11.7
6-10 years	59	19.7
11-15 years	51	17.0
More than 15 years	123	41.0
Prefer not to answer	2	0.7
Question 35: What is your medical specialty?		
Oncology	72	24.0
Primary Care	19	6.3
Pain Management	152	50.7
Other (please specify)[1]	57	19.0
No designated specialty	0	0.0

Table 4. Description of Eligible Prescribers

Question	Eligible Completed Prescribers N=300[3]	
	n	%
Question 34: In which state or US territory do you practice?		
Northeast[2]	76	25.3
Midwest[2]	44	14.7
South[2]	96	32.0
West[2]	83	27.7
Other[2]	0	0.0
Prefer not to answer	1	0.3

[1] Other medical specialties are presented in Appendix B, Listing 2.

[2] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[3] Number of eligible prescribers completing the survey (See Table 1).

5.1.3 TIRF Medicines Educational Materials

Prescribers were asked about their access to educational materials for TIRF medicines, specifically the Full Prescribing Information, the Medication Guide, and the Patient-Prescriber Agreement Form (PPAF) (Table 5). Almost all prescribers reported they had received or had access to the Full Prescribing Information (n=292; 97.3%) and the Medication Guide (n=283; 94.3%). Of those with access to these materials, 83.9% indicated that they had read the Full Prescribing Information and 91.2% indicated that they had read the Medication Guide. Additionally, most prescribers reported reviewing the PPAF with each patient or their caregiver (89.0%); signing the PPAF and having the patient/caregiver sign the PPAF (91.4%); and giving a copy of the PPAF to the patient (82.0%). The verbatim responses (Appendix B, Listing 1) included requests for guides, information on dosage, conversion, and titration, continuing TIRF medicines if patient stops taking around-the-clock opioid, and drug interference with erythromycin.

Table 5. Responses to Questions About the TIRF Medicines Educational Materials and the TIRF Patient-Prescriber-Agreement Form

Question	Eligible and Complete Respondents N=300[3]	
	N	%
Question 20: Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you prescribe?		
Yes	292	97.3
No	2	0.7
I don't know	6	2.0
Question 21: Did you read the Full Prescribing Information for the TIRF medicine(s) that you prescribe?[1]		
Yes	245	83.9
No	40	13.7
I don't know	7	2.4
N/A (answered ***No*** or ***I don't know*** to Question 20)	8	
Question 22: Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you prescribe?		
Yes	283	94.3
No	5	1.7
I don't know	12	4.0
Question 23: Did you read the Medication Guide for the TIRF medicine(s) that you prescribe?[1]		
Yes	258	91.2
No	20	7.1
I don't know	5	1.8
N/A (answered ***No*** or ***I don't know*** to Question 22)	17	
Question 24: Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?		
Yes[2]	39	13.0
No	247	82.3
I don't know	14	4.7

Table 5. Responses to Questions About the TIRF Medicines Educational Materials and the TIRF Patient-Prescriber-Agreement Form

Question	Eligible and Complete Respondents N=300[3]	
	N	%
Question 26: Do you review the Patient-Prescriber Agreement Form with each of your patients for whom you prescribe TIRF medicines or their caregiver?		
Yes	267	89.0
No	27	9.0
I don't know	6	2.0
Question 27: Do you and the patient or their caregiver sign the Patient-Prescriber Agreement Form for TIRF medicines after you have reviewed it with him/her? [1]		
Yes	244	91.4
No	16	6.0
I don't know	7	2.6
N/A (answered ***No*** or ***I don't know*** to Question 26)	33	
Question 28: Do you give a copy of the Patient-Prescriber Agreement Form for TIRF medicines to the patient or their caregiver?		
Yes	246	82.0
No	40	13.3
I don't know	14	4.7

[1] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[2] Verbatim texts for questions about the information in the Full Prescribing Information or Medication Guide are presented in Appendix B, Listing 1.
[3] Number of eligible prescribers completing the survey (See Table 1).
N/A = Not Applicable

5.2 KAB Survey Objectives

5.2.1 Key Risk Message Results

The focus of this section of the document is on the findings for the total eligible respondent population who completed the survey. A summary of results by sub-group are described in a separate section of this document, Section 5.2.3.

5.2.1.1 Key Risk Message 1

Key Risk Message 1 referred to the prescriber's knowledge of TIRF medicine contraindication in opioid non-tolerant patients.

Analysis of responses to components of Question 5 for Key Risk Message 1 showed that a high percentage of prescribers are aware that patients with cancer who are considered opioid-tolerant are those who are taking around-the-clock opioid therapy for cancer pain for one week or longer (270, 90.0%) and are those who are currently taking opioid therapy (261, 87.0%). Additionally most prescribers (260, 86.7%) understood that TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur, and that death has occurred in opioid non-tolerant patients treated with some fentanyl products (287; 95.7%). Most prescribers were aware patients just starting a TIRF medicine must begin with titration from the lowest available dose for that product (252; 84.0%) and that TIRF medicines may not be used to treat opioid non-tolerant patients (246; 82.0%), (Table 6). Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 6.1 out of 7.

Table 6. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible Completed Prescribers N=300[1]	
	N	% (95% CI)[3]
Question 5: Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:		
5a: Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer[5]		
True[1]	270	90.0 (86.0, 93.2)
False	22	7.3
I don't know	8	2.7
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before		
True	24	8.0
False[1]	261	87.0 (82.7, 90.6)
I don't know	15	5.0

Table 6. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible Completed Prescribers N=300[1]	
	N	% (95% CI)[3]
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy		
True	28	9.3
False[1]	259	86.3 (81.9, 90.0)
I don't know	13	4.3
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.		
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True[1]	260	86.7 (82.3, 90.3)
False	32	10.7
I don't know	8	2.7
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True[1]	287	95.7 (92.7, 97.7)
False	2	0.7
I don't know	11	3.7
7c: TIRF medicines may be used to treat opioid non-tolerant patients.		
True	46	15.3
False[1]	246	82.0 (77.2, 86.2)
I don't know	8	2.7
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.		
True[1]	252	84.0 (79.4, 88.0)
False	42	14.0
I don't know	6	2.0

Table 6. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible Completed Prescribers N=300[1]	
	N	% (95% CI)[3]
Secondary Analysis: Average Number of Correct Responses		
0 correct responses	0	0.0
1 correct response	1	0.3
2 correct responses	4	1.3
3 correct responses	8	2.7
4 correct responses	15	5.0
5 correct responses	39	13.0
6 correct responses	84	28.0
7 correct responses	149	49.7
Average number of correct responses	6.1	(5.9, 7.0)[2]

[1] Indicates the correct response(s) to each question or item within a question.

[2] One-sided 95% confidence intervals using the normal approximation to the Poisson distribution

[3] All confidence intervals are exact binomial 95% confidence intervals.

[4] Number of eligible prescribers completing the survey (See Table 1).

5.2.1.2 Key Risk Message 2

Key Risk Message 2 referred to the prescriber's knowledge of the indications for prescribing TIRF medicines for the management of breakthrough pain in opioid-tolerant adult cancer patients.

Table 7 presents the responses to components of Question 9 (*In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients?*) for Key Risk Message 2. Of the 300 eligible respondents, 288 (96.0%) prescribe TIRF medicines for breakthrough pain from cancer. In addition, most prescribers do not prescribe TIRF medicines for other painful conditions such as acute or postoperative pain (87.3%), headache or migraine pain (89.7%), dental pain (97.3%), or for chronic non-cancer pain (62.0%). However, 112 (37.3%) prescribers stated that they prescribe TIRF medicines for chronic non-cancer pain.

In addition, Table 7 presents responses to components of Question 13 (*The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option*) for Key Risk Message 2. Of the 300 eligible respondents, 199 (66.3%)

responded with the correct response that a TIRF medicine should only be prescribed to an adult female with localized breast cancer who just completed a mastectomy and reconstructive surgery and who has persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.

Overall, evidence of understanding of the comprehensive key risk message is supported by the average number of correct responses identified as 5.0 out of 6.

Table 7. Responses Linked to Key Risk Message 2: TIRF Medicines Are Only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (16 Years of Age and Older for Actiq® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible Completed Prescribers N=300[4]	
	n	% (95% CI)[3]
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.		
9a: Acute or postoperative pain		
Yes	37	12.3
No[1]	262	87.3 (83.0, 90.9)
I don't know	1	0.3
9b: Headache or migraine pain		
Yes	31	10.3
No[1]	269	89.7 (85.7, 92.9)
I don't know	0	0.0
9c: Dental pain		
Yes	8	2.7
No[1]	292	97.3 (94.8, 98.8)
I don't know	0	0.0
9d: Breakthrough pain from cancer		
Yes[1]	288	96.0 (93.1, 97.9)
No	12	4.0
I don't know	0	0.0

Table 7. Responses Linked to Key Risk Message 2: TIRF Medicines Are Only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (16 Years of Age and Older for Actiq® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible Completed Prescribers N=300[4]	
	n	% (95% CI)[3]
9e: Chronic non-cancer pain		
Yes	112	37.3
No[1]	186	62.0 (56.2, 67.5)
I don't know	2	0.7
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.		
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks. [1]	199	66.3 (60.7, 71.7)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	30	10.0
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	19	6.3
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	22	7.3
I don't know	30	10.0
Secondary Analysis: Average Number of Correct Responses		
0 correct response	0	0.0
1 correct response	3	1.0
2 correct responses	4	1.3
3 correct responses	20	6.7
4 correct responses	48	16.0

Table 7. Responses Linked to Key Risk Message 2: TIRF Medicines Are Only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (16 Years of Age and Older for Actiq® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible Completed Prescribers N=300[4]	
	n	% (95% CI)[3]
5 correct responses	117	39.0
6 correct responses	108	36.0
Average Number of Correct Responses	5.0	(4.8, 6.0)[2]

[1] Indicates the correct response(s) to each question or item within a question.
[2] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution
[3] All confidence intervals are exact binomial 95% confidence intervals.
[4] Number of eligible prescribers completing the survey (See Table 1).

5.2.1.3 Key Risk Message 3

Key Risk Message 3 refers to prescribers' knowledge of risk factors and signs and symptoms of opioid abuse in patients who take TIRF medicines.

Responses to components of Question 7, 8, and 10 for Key Risk Message 3 showed that a high percentage of prescribers were aware that it is important to monitor for signs of abuse and addiction in patients who take TIRF medicines (299, 99.7%), that a personal history of psychiatric illness is a risk factor for opioid abuse (252, 84.0%), that a personal history of past or current alcohol or drug abuse or a family history of drug and alcohol abuse is a risk factor for opioid abuse (299, 99.7%), and that TIRF medicines can be abused in a manner similar to other opioid agonists (292, 97.3%). Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 3.8 out of 4 (Table 8).

Table 8. Responses Linked to Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist, and a Schedule II Controlled Substance, With Abuse Liability Similar to Other Opioid Analgesics.

Question	Eligible Completed Prescribers N=300[4]	
	n	% (95% CI)[3]
Question 7: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.		
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True[1]	299	99.7 (98.2, 100.0)
False	1	0.3
I don't know	0	0.0
Question 8: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.		
8a: A personal history of psychiatric illness		
Yes[1]	252	84.0 (79.4, 88.0)
No	23	7.7
I don't know	25	8.3
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes[1]	299	99.7 (98.2, 100.0)
No	1	0.3
I don't know	0	0.0
Question 10: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.		
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True[1]	292	97.3 (94.8, 98.8)
False	7	2.3
I don't know	1	0.3
Secondary Analysis: Demonstrated Understanding		
0 correct responses	0	0.0
1 correct response	0	0.0
2 correct responses	5	1.7

Table 8. Responses Linked to Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist, and a Schedule II Controlled Substance, With Abuse Liability Similar to Other Opioid Analgesics.

Question	Eligible Completed Prescribers N=300[4]	
	n	% (95% CI)[3]
3 correct responses	48	16.0
4 correct responses	247	82.3
Average number of correct responses	3.8	(3.6, 4.0)[2]

[1] Indicates the correct response(s) to each question or item within a question.
[2] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.
[3] All confidence intervals are exact binomial 95% confidence intervals.
[4] Number of eligible prescribers completing the survey (See Table 1).

5.2.1.4 Key Risk Message 4

Key Risk Message 4 refers to prescriber's knowledge that TIRF Medicines are not interchangeable with each other, regardless of route of administration.

Responses to components of Questions 10 and 14 for Key Risk Message 4 are presented in Table 9. The analysis of responses showed that 279 (93.0%) prescribers understood that TIRF medicines are not interchangeable with each other regardless of the route of administration, that the conversion of one TIRF medicine to another may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption (290; 96.7%), and that dosing of different TIRF medicines is not equivalent on a microgram-to-microgram basis (272; 90.7%). Question 14 dealt with the course of action prescribers must adopt in converting a patient from one TIRF medicine to another. In response, 223 (74.3%) prescribers correctly responded that conversion must not be done on a microgram-to-microgram basis because of differences in absorption kinetics. Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 3.5 out of 4.

Table 9. Responses Linked to Key Risk Message 4: TIRF Medicines Are Not Interchangeable With Each Other, Regardless of Route of Administration.

Question	Eligible Completed Prescribers N=300[4]	
	n	% (95% CI)[3]
Question 10: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.		
10b: TIRF medicines are interchangeable with each other regardless of route of administration.		
True	15	5.0
False[1]	279	93.0 (89.5, 95.6)
I don't know	6	2.0
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.		
True[1]	290	96.7 (94.0, 98.4)
False	6	2.0
I don't know	4	1.3
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True[1]	272	90.7 (86.8, 93.7)
False	18	6.0
I don't know	10	3.3
14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.		
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose. [1]	223	74.3 (69.0, 79.2)
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	26	8.7
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	3	1.0

Table 9. Responses Linked to Key Risk Message 4: TIRF Medicines Are Not Interchangeable With Each Other, Regardless of Route of Administration.

Question	Eligible Completed Prescribers N=300[4]	
	n	% (95% CI)[3]
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	32	10.7
I don't know	16	5.3
Secondary Analysis: Demonstrated Understanding		
0 correct responses	2	0.7
1 correct response	7	2.3
2 correct responses	18	6.0
3 correct responses	71	23.7
4 correct responses	202	67.3
Average number of correct responses	3.5	(3.4, 4.0)[2]

[1] Indicates the correct response(s) to each question or item within a question.
[2] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.
[3] All confidence intervals are exact binomial 95% confidence intervals.
[4] Number of eligible prescribers completing the survey (See Table 1).

5.2.2 Other Survey Questions

5.2.2.1 Additional Questions about TIRF Medicines Safety

Overall, 10 questions containing 30 components assessed prescribers' understanding about the safe use of TIRF medicines (Table 10). Some of the concepts of safe use were also included within the questions/statements included under the 4 key risk messages and are not included here (See Section 5.2.1).

The overall results of safety analyses demonstrated that most prescribers were aware of the safe use of TIRF medicines requirements. Sixty percent (n=180) of the prescribers surveyed correctly identified that a cancer patient should not be started on a TIRF medicine and an around-the-clock opioid at the same time, while 101 (33.7%) prescribers responded that this is acceptable. In addition, 179 (59.7%) responded that patients should not continue to take TIRF medicines if they stop taking their around-the-clock opioid medicine. As part of behavior assessment, the same concept was tested under Question 18c and elicited the desired "False" response from 61.0% (n=183) of prescribers. Of the 300 prescribers who completed the survey, 211 (70.3%) prescribers correctly indicated that a cancer patient who

has been on an around-the-clock opioid for one day should not start taking a TIRF medicine for breakthrough pain (Table 10).

A majority of prescribers (270; 90.0%) correctly answered that opioid-tolerant patients are those who are taking regular opioid therapy for 1 week or longer (Table 6). The proportion of prescribers who correctly identified the doses of individual TIRF medicines given for 1 week or longer as a basis for considering patients as opioid-tolerant were 70.3% for 8 mg oral hydromorphone/day, 92.3% for 60 mg oral morphine/day, 78.0% for 30 mg/day oral oxycodone, 83.7% for 25 mcg transdermal fentanyl/hour, 74.7% for 25 mg/day oral oxymorphone, and 59.0% for an equianalgesic dose of another oral opioid (Table 10).

Most prescribers (267; 89.0%) correctly indicated that for a patient starting a TIRF medicine, an appropriate dose is the lowest available dose, unless the Full Prescribing Information provides specific guidance (Table 10). For the same concept asked as a part of Key Risk Message 1 (*Question 7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine*), the correct response was given by 84.0% of prescribers (Table 6). When presented with the scenario (Question 16) of a patient who has started on the lowest dose of a TIRF medicine, and, after 30 minutes, the breakthrough pain has not been sufficiently relieved, 199 (66.3%) prescribers correctly responded that they should follow the guidance based on the product-specific Medication Guide because the recommendations are not the same for all TIRF medicines. The majority (272, 90.7%) of prescribers correctly indicated that the dosages of TIRF medicines are not equivalent on a microgram-to-microgram basis (Table 10).

The majority (232, 77.3%) of prescribers indicated a high level of understanding of the safe use of a TIRF medicine with a CYP3A4 inhibitor including the possibility that a dosage adjustment may be required, and the need to monitor the patient for opioid toxicity to avoid the potential for fatal respiratory depression (Table 10). Nearly all prescribers surveyed (298, 99.3%) understood that TIRF medicines contain fentanyl in an amount that could be fatal for children of all ages, for individuals for whom they were not prescribed, and for those who are not opioid tolerant. Most prescribers (272, 90.7%) were aware that patients must be informed that TIRF medicines should not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain. In addition, 297 (99.0%) respondents understood that patients must be instructed not to share their TIRF medicine with anyone else, even if that person has the same symptoms. However, 59.7% (179) prescribers were aware that if patients stopped taking their around the clock opioid pain medicine, they must stop taking their TIRF medicine.

Table 10. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Prescribers N=300[2]	
	n	%
Question 6: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.		
6a: A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time.		
True	101	33.7
False[1]	180	60.0
I don't know	19	6.3
6b: A cancer patient who has been on an around-the-clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.		
True	68	22.7
False[1]	211	70.3
I don't know	21	7.0
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.		
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True[1]	287	95.7
False	2	0.7
I don't know	11	3.7
Question 8: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.		
8c: A family history of asthma		
Yes	14	4.7
No[1]	268	89.3
I don't know	18	6.0

Table 10. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Prescribers N=300[2]	
	n	%
Question 10: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.		
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True[1]	272	90.7
False	18	6.0
I don't know	10	3.3
Question 11: Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:		
11a: 8 mg oral hydromorphone/day		
True[1]	211	70.3
False	66	22.0
I don't know	23	7.7
11b: 60 mg oral morphine/day.		
True[1]	277	92.3
False	42	14.0
I don't know	12	4.0
11c: 30 mg oral oxycodone/day		
True[1]	234	78.0
False	42	14.0
I don't know	24	8.0
11d: 25 mcg transdermal fentanyl/hour		
True[1]	251	83.7
False	31	10.3
I don't know	18	6.0
11e: 25 mg oral oxymorphone/day		
True[1]	224	74.7
False	41	13.7

Table 10. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Prescribers N=300[2]	
	n	%
I don't know	34	11.7
11f: An equianalgesic dose of another oral opioid		
True[1]	177	59.0
False	66	22.0
I don't know	57	19.0
Question 15: A patient is starting titration with a TIRF medicine. What dose must they start with? Please select one option.		
15a. An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.	28	9.3
15b. The dose that the prescriber believes is appropriate based on their clinical experience.	5	1.7
15c. The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.[1]	267	89.0
15d. The median available dose.	0	0.0
15e. I don't know.	0	0.0
Question 16: A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do? Please pick the best option of the scenarios described.		
16a. Take another (identical) dose of the TIRF medicine immediately.	77	25.7
16b. Take a dose of an alternative rescue medicine.	17	5.7
16c. Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines. [1]	199	66.3
16d. Double the dose and take immediately.	4	1.3
16e. I don't know.	3	1.0

Table 10. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Prescribers N=300[2]	
	n	%
Question 17: A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please pick the best option of the scenarios described.		
17a: The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.	7	2.3
17b: Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.[1]	232	77.3
17c: There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.	7	2.3
17d: The dose of the TIRF medicine must be reduced by one-half if a CYP3A4 inhibitor is prescribed in the same patient.	11	3.7
17e: I don't know.	43	14.3
Question 18: Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select "True," "False," or "I don't know" for each of the following counseling statements.		
18a: TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.		
True[1]	298	99.3
False	0	0.0
I don't know	2	0.7
18b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.		
True[1]	272	90.7
False	16	5.3
I don't know	12	4.0

Table 10. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Prescribers N=300[2]	
	n	%
18c: Instruct patients that, if they stop taking their around-the-clock opioid medicine, they can continue to take their TIRF medicine.		
True	89	29.7
False[1]	183	61.0
I don't know	28	9.3
18d: Instruct patients never to share their TIRF medicine with anyone else, even if that person has the same symptoms.		
True[1]	297	99.0
False	2	0.7
I don't know	1	0.3
Question 19: Can patients continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine?		
Yes	96	32.0
No[1]	179	59.7
I don't know.	25	8.3

[1] Indicates the correct response(s) to each question or item within a question.
[2] Number of eligible prescribers completing the survey (See Table 1).

5.2.2.2 Prescriber Activities When Prescribing TIRF Medicines

Prescribers were asked about specific activities performed when prescribing TIRF medicines (Table 11).

More than one-half of prescribers (56.3%) indicated they always ask patients (or their caregivers) about the presence of children in the home (Question 12a). When asked about counseling patients/caregivers that accidental exposure to TIRF medicines by a child might be fatal, 204 (68.0%) prescribers selected "always", 66 (22.0%) responded "only with first prescription", and 26 (8.7%) answered "sometimes". In response to the question about instructing patients/caregivers to keep TIRF medicines out of the reach of children, 223 (74.3%) selected "always," 52 (17.3%) selected "only with the first prescription," and 22 (7.3%) selected "sometimes." The safe use surveillance (Table 10) demonstrated that 298 (99.3%) prescribers were aware that TIRF medicines contain fentanyl in an amount that

could be fatal to children of all ages (Question 18). The majority of prescribers indicated they always instruct patients (or their caregivers) not to share TIRF medicines (235; 78.3%). With regard to instructing patients/caregivers about proper disposal of any unused or partially used TIRF medicines, 186 (62.0%) answered "always," 68 (22.7%) answered "only with the first prescription," and 38 (12.7%) responded "sometimes."

Less than one-half of prescribers (42.3%) always give patients/caregivers the Medication Guide for their TIRF medicine, and 41.3% give their patients/caregivers the Medication Guide for their TIRF medicine only with the first prescription.

Table 11. Responses to All Questions About Activities When Prescribing TIRF Medicines

Question	Eligible Completed Prescribers N=300[1]	
	n	%
Question 12: How frequently do you perform the following activities when prescribing TIRF medicines? Please answer "Always," "Only with the first prescription," "Sometimes," "Never," or "I don't know."		
12a: Ask patients (or their caregivers) about the presence of children in the home.		
Always	169	56.3
Only with the first prescription	81	27.0
Sometimes	42	14.0
Never	7	2.3
I don't know	1	0.3
12b: Instruct patients (or their caregivers) not to share TIRF medicines with anyone else.		
Always	235	78.3
Only with the first prescription	41	13.7
Sometimes	17	5.7
Never	6	2.0
I don't know	1	0.3
12c: Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal.		
Always	204	68.0
Only with the first prescription	66	22.0
Sometimes	26	8.7
Never	3	1.0

Table 11. Responses to All Questions About Activities When Prescribing TIRF Medicines

Question	Eligible Completed Prescribers N=300[1]	
	n	%
I don't know	1	0.3
12d: Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure.		
Always	223	74.3
Only with the first prescription	52	17.3
Sometimes	22	7.3
Never	2	0.7
I don't know	1	0.3
12e: Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines.		
Always	186	62.0
Only with the first prescription	68	22.7
Sometimes	38	12.7
Never	7	2.3
I don't know	1	0.3
12f: Give patients (or their caregivers) the Medication Guide for their TIRF medicine.		
Always	127	42.3
Only with the first prescription	124	41.3
Sometimes	35	11.7
Never	11	3.7
I don't know	3	1.0

[1] Number of eligible prescribers completing the survey (See Table 1).

5.2.3 Sub-group Analysis of Responses to Key Risk Messages

To assess further prescribers' understanding of key risk messages, sub-group analyses as described in Section 4.1.2 were conducted. Prescribers who read the *Medication Guide* and the *Full Prescribing Information* had greater understanding based on their correct responses to questions/statements under Key Risk Messages 1, 3, and 4 compared with those who had not received or read these education materials. For Key Risk Message 2, the percentages of prescribers who provided all 6 correct responses to the questions/statements under the key

risk message were 37.1% among those who read the education materials and 27.3% among those who had not read or received the education materials.

Overall, respondents who completed the survey via telephone, had a lower rate for correct responses for Key Risk Message 1 and both Internet and telephone users had low rates of correct responses for Key Risk Message 2 compared with all correct response rates for other key risk messages (Table 12). The full set of sub-group analysis tables is provided in Appendix B.

Table 12. Percentage of All Correct Responses to Key Risk Messages based on Sub-Groups 1 and 5 - Sub-Group Analysis 1: Reading Medication Guide or full Prescribing Information - Sub-Group Analysis 5: Modality to Complete Survey

Key Risk Message	Sub-Group Analysis 1: Reading Medication Guide or full Prescribing Information				
	Number of questions	Received and Read the Education Materials		Not Received or Not Read the Education Materials	
		Percentage of Respondents with All Correct Responses (%)	Average Number of Correct Responses[1]	Percentage of Respondents with All Correct Responses (%)	Average Number of Correct Responses[1]
1	7	52.8	6.2 (5.9, 7.0)	24.2	5.6 (4.9, 7.0)
2	6	37.1	5.0 (4.8, 6.0)	27.3	4.8 (4.2, 6.0)
3	4	83.9	3.8 (3.6, 4.0)	69.7	3.7 (3.1, 4.0)
4	4	69.3	3.6 (3.4, 4.0)	51.5	3.3 (2.8, 4.0)
	Sub-Group Analysis 5: Modality to Complete Survey				
Key Risk Message	Number of questions	Internet		Telephone	
		Percentage of Respondents with All Correct Responses (%)	Average Number of Correct Responses[1]	Percentage of Respondents with All Correct Responses (%)	Average Number of Correct Responses[1]
1	7	50.4	6.1 (5.9, 7.0)	38.9	5.6 (4.7, 7.0)
2	6	36.9	5.0 (4.8, 6.0)	22.2	4.8 (3.9, 6.0)
3	4	83.7	3.8 (3.6, 4.0)	61.1	3.6 (2.8, 4.0)
4	4	68.1	3.6 (3.4, 4.0)	55.6	3.4 (2.7, 4.0)

[1] One-sided 95% CI using the normal approximation to the Poisson distribution

5.3 Spontaneous Reporting of Adverse Events, Product Complaints or Medical Information Requests

Among all survey respondents (N=300, Table 1), there were no adverse events or product complaints reported. In the Internet survey, respondents had the option to write in any

questions they had when asked, "*What are your questions*?" Respondents who took the telephone survey could have spontaneously asked a question. This resulted in 35 individual responses by various completers, of which 12 were requests for medical information and 11 were indications that the free text field was not applicable or they had no questions. (Appendix B, Listing 1).

5.4 Summary of Correct Responses for Key Risk Messages

The four key risk messages of the survey included 21 components detailing these key risk messages. A tabulated summary of correct/desired response proportions to each component is presented below (Table 13). The correct response rate was greater than or equal to 95% for 7 components, between 80% but <95% for 11 components, greater than 70% but less than 80% for one component, and less than 70% for 2 of the components of the key risk messages.

Question 9 (*In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients?*) containing 5 components assessed prescribers' behavior pattern regarding their choice of clinical conditions for which they prescribe TIRF medicines. The majority of eligible respondents (n=288; 96.0%) selected the desired response of breakthrough pain from cancer. The responses do identify that in general, prescribers *do not* prescribe TIRF medicines for acute or postoperative pain (n=262; 87.3%), headache or migraine pain (n=269; 89.7%), dental pain (n=292; 97.3%), and chronic non-cancer pain (n=186; 62.0%). (Table 13).

Question 13 presented prescribers with a scenario of four cases describing patients experiencing breakthrough pain and asked prescribers to identify the case that should not receive TIRF medicine; 199 (66.3%) prescribers correctly identified the patient for whom a TIRF medicine was not appropriate (*Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks*).

Table 13. Summary of Correct Responses for Key Risk Messages

Question #	Question	Response Rates	
		N	% (95% CI)
Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients			
5. Patients with cancer who are considered opioid-tolerant are those:			
5a	Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer (*Correct Response True*)	270	90.0 (86.0, 93.2)
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before (*Correct Response False*)	261	87.0 (82.7, 90.6)
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy (*Correct Response False*)	259	86.3 (81.9, 90.0)
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose (*Correct Response True*)	260	86.7 (82.3, 90.3)
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products (*Correct Response True*)	287	95.7 (92.7, 97.7)
7c	TIRF medicines may be used to treat opioid non-tolerant patients (*Correct Response False*)	246	82.0 (77.2, 86.2)
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine (*Correct Response True*)	252	84.0 (79.4, 88.0)
Key Risk Message 2: TIRF Medicines are only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (16 Years of Age and Older for Actiq® Brand and Generic Equivalents) who are already Receiving and who are Tolerant to Around-the-Clock Opioid Therapy for their Underlying Persistent Cancer Pain			
9. In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients?			
9a	Acute or postoperative pain (*Desired Behavior response "No"*)	262	87.3 (83.0, 90.9)
9b	Headache or migraine pain (*Desired Behavior response "No"*)	269	89.7 (85.7, 92.9)

Table 13. Summary of Correct Responses for Key Risk Messages

Question #	Question	Response Rates	
		N	% (95% CI)
9c	Dental pain (*Desired Behavior response "No"*)	292	97.3 (94.8. 98.8)
9d	Breakthrough pain from cancer (*Desired Behavior response 'Yes'*)	288	96.0 (93.1, 97.9)
9e	Chronic non-cancer pain (*Desired Behavior response "No"*)	186	62.0 (56.2, 67.5)
13. The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine?			
13b	Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks (*Correct Response*)	199	66.3 (60.7, 71.7)
Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist and a Schedule II Controlled Substance, with Abuse Liability Similar to other Opioid Analgesics			
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines *(Correct Response True*)	299	99.7 (98.2, 100.0)
8. Which of the following are risk factors for opioid abuse?			
8a	A personal history of psychiatric illness (*Correct Response Yes*)	252	84.0 (79.4, 88.0)
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse (*Correct Response Yes*)	299	99.7 (98.2, 100.0)
10a	TIRF medicines can be abused in a manner similar to other opioid agonists (*Correct Response True*)	292	97.3 (94.8, 98.8)
Key Risk Message 4: TIRF Medicines are not Interchangeable with each other, Regardless of Route of Administration			
10b	TIRF medicines are interchangeable with each other regardless of route of administration (*Correct Response False*)	279	93.0 (89.5, 95.6)

Table 13. Summary of Correct Responses for Key Risk Messages

Question #	Question	Response Rates	
		N	% (95% CI)
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption (*Correct Response True*)	290	96.7 (94.0, 98.4)
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (*Correct Response True*)	272	90.7 (86.8, 93.7)
14. A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed?			
14b	The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose (*Correct Response*).	223	74.3 (69.0, 79.2)

6. FDA FEEDBACK

FDA provided the following feedback on the 24-month assessment of the TIRF REMS, which was received in August 2014. This feedback was received too late to incorporate changes into the 36-month prescriber KAB survey but changes based on FDA feedback will be incorporated into the 48-month prescriber KAB survey.

- In your prescriber survey, only 59% correctly stated that TIRF should not be used to treat "chronic non-cancer pain." It is not clear if this represents a knowledge deficit or a disagreement with how these medicines should be used. In the next survey, include a supplemental question directed at those who respond incorrectly to this question to follow-up as to why they feel that this is an appropriate use of TIRFs.

- In future surveys of prescribers, report the proportion of prescriber respondents that work in closed systems.

7. DISCUSSION AND CONCLUSIONS

Discussion

For the prescriber KAB survey invitations (and reminders) were sent to a random sample of prescribers enrolled in the TIRF REMS Access Program. From among those who responded to the invitation, 300 prescribers completed the survey; thus, the program sample size was achieved within the specific period.

The specific goals of the TIRF medicines prescriber KAB survey were to assess prescribers' understanding of the risks associated with TIRF medicine use, the selection of appropriate patients for treatment with TIRF medicines, preventing inappropriate conversion between TIRF medicines, and ensuring safe use of TIRF medicines while preventing exposure to children and others for whom TIRF medicines were not prescribed.

In the 36-month prescriber KAB survey, of the 21 components of the 4 key risk messages, only 1 component had a response rate less than the desired threshold of 65%. As a measure of prescribers' behavior, 62.0% (n=186) of respondents gave the desired response "No" to Question 9 (*In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Component 9e: Chronic non-cancer pain*). The response from prescribers regarding the desired response that TIRF medicines are not prescribed for non-cancer pain has been consistently low for all 3 surveys (Wave 1: 54.3%; Wave 2: 58.9%; Wave 3: 62.0%) as listed in Table 14. Based on FDA feedback an additional question will be added to the 48-month survey asking prescribers why they feel this is an appropriate use of a TIRF medicine. For the other 4 components of Question 9, the desired responses were greater than 87% in the 36-month survey.

In addition, for 4 other questions that assessed prescribers' understanding/behavior concerning the safe use of TIRF medicines, the correct/desired responses were less than the threshold of 65%. The details of the low scoring components of questions under key risk messages and safe use of TIRF medicines questions are listed in Table 14.

The correct response rate for Component 6a which addresses knowledge that a cancer patient should not be started on a TIRF medicine and an around-the-clock opioid at the same time was 60.0%. This concept also scored low for pharmacists (63.3%). This concept also scored low for pharmacists (63.3%) during this reporting period. However, component 6b (*A cancer patient who has been on an around-the-clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain*) under Question 6 elicited a correct response rate of 70.3%.

In response to Question 11, (*Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:*), the desired option 11f (*An equianalgesic dose of another oral opioid*) was selected by 59.0% (n=177) of prescribers (Table 14). The desired response in Wave 2 was selected by 65.9%; the question was not asked in Wave 1. For this reporting period, pharmacists also had a similar low rate of correct response for this concept (59.0%).

The desired response of 'False'for component 18c which assessed prescriber behavior (*Instruct patients that, if they stop taking their around -the-clock opioid medicine, they can continue to take their TIRF medicine)* and the correct response for Question 19 which assessed prescriber knowledge (*Can patients continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine?*) was 61.0%, and 59.7%, respectively. This concept also scored low in the patient KAB survey for this reporting period.

Correct response rates were consistently low for components 6a and 11f between the 24-month and 36-month Prescriber KAB surveys. The correct/desired responses for components 9e (behavior assessment),18c (behavior assessment) and 19 (knowledge assessment) were low across all Prescriber KAB surveys (Table 14).

Table 14. Desired Response of Low Scoring Questions Across the Three Prescriber KAB Survey Waves.

36-Month Survey Question Number	Questions as Presented in the 36-Month Survey	12-Month Survey Desired Response (%)	24-Month Survey Desired Response (%)	36-Month Survey Desired Response (%)	Link to Table in this document
6[1]	**Please answer True, False, or I don't know to each statement based on the labeling for TIRF medicines**				
6a[1]	A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time (***Desired Response: False***)	**Not asked**	**60.6**	**60.0**	Table 10
9[2]	**In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.**				
9e[2]	Chronic non-cancer pain (***Desired Response: No***)	54.3[1]	58.9	62.0	Table 7
11[1]	**Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:**				
11f[1]	An equianalgesic dose of another oral opioid (***Desired Response: True***)	**Not asked**	**65.9**	**59.0**	Table 10
18[1]	**Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements:**				
18c[1]	Instruct patients that, if they stop taking their around -the-clock opioid medicine, they can continue to take their TIRF medicine (***Desired Response: False***)	**68.5**	**57.9**	**61.0**	Table 10
19[1]	**Can patients continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine?**				
19[1]	Can patients continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine? (***Desired Response: No***)	**68.5**	**53.0**	**59.7**	Table 10

[1] Not asked as a key risk message.

[2] This was part of Question 8 (8e) in 12-month Prescriber KAB survey. Question 8 was worded as follows for the 12-month KAB survey: For which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.

Although the correct/desired response rate for components in Table 14 are below the desired threshold of 65%, the rates for components within the same questions or for similar concepts are high. Although the majority of the respondents scored less than the desired threshold of 65% in component 6a, 70.3% of the respondents understood a cancer patient who had been on an around-the-clock opioid for one day should not start taking a TIRF medicine for breakthrough pain (Component 6b). In addition, the majority of the respondents (90.0%) indicated patients with cancer who are considered opioid tolerant are those who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer (Component 5a, Key Risk Message 1). In response to Question 11, which also addresses opioid tolerance by asking the respondent to identify specific medications and doses that if taken by a patient for one week or longer would identify that the patient as opioid tolerant, most of the respondents (>70%) identified a desired response for all components; however, component 11f (*equianalgesic dose of another oral opioid)* having a low response of 59.0%.

Conclusions

The consistently high level of prescriber understanding of key risk messages in the 24-month and 36-month surveys indicates that the Education Program for Prescribers and Pharmacists is meeting the goals of the TIRF REMS. The TRIG will evaluate the concepts that have scored low among stakeholders to determine if any action is warranted. As stated above, changes will be implemented into the 48-month Prescriber KAB survey based on FDA feedback received on the 24-month TIRF REMS assessment report. The TRIG will continue to work with the FDA to refine, on a continual basis, the steps to mitigate risks associated with TIRF medicines.

Appendix A Prescriber Survey Protocol

PROTOCOL TITLE:	**Quantitative Testing of Prescriber Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)** **Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)** **Depomed, Inc.** **Galena Biopharma, Inc.** **Insys Therapeutics** **Mallinckrodt Pharmaceuticals** **Meda Pharmaceuticals** **Mylan, Inc.** **Par Pharmaceutical, Inc.**
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TABLE OF CONTENTS PAGE

	TABLE OF CONTENTS	2
1.	LIST OF ABBREVIATIONS	3
2.	BACKGROUND	4
3.	OBJECTIVES OF THE EVALUATION SURVEY	5
4.	METHODS	5
4.1	Survey Design	5
4.1.1	Qualitative Research on the Survey	6
4.1.2	Questions on REMS Goals	6
4.1.3	Additional Questions	9
4.2	Participant Recruitment	9
4.2.1	Measures to Minimize Bias in the Sample	10
5.	STUDY POPULATION	10
5.1.1	Sample Size	10
5.1.2	Inclusion Criteria	11
5.1.3	Exclusion Criteria	11
6.	SURVEY PROCESS	11
6.1	Screening and Survey Administration	11
6.1.1	Telephone	12
6.1.2	Internet	12
6.2	Measures to Minimize Bias in the Survey Process	12
7.	ANALYSIS	12
7.1.1	Analysis Population	13
7.1.2	Description of Primary Analyses	13
7.1.3	Description of Secondary Analyses	13
8.	SAFETY EVENT REPORTING	14
9.	PRIVACY PROTECTION AND CONFIDENTIALITY	14

LIST OF APPENDICES

Appendix A	Prescriber Questionnaire	15
Appendix B	SAMPLE Prescriber Invitation Letter	37

1. LIST OF ABBREVIATIONS

CATI	Computer-Assisted Telephone Interviewing
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ISI	Important Safety Information
KAB	Knowledge, Attitudes and Behavior
PI	Prescribing Information
REMS	Risk Evaluation and Mitigation Strategy
SE PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access Program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by the following:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

2. Preventing inappropriate conversion between TIRF medicines.

3. Preventing accidental exposure to children and others for whom it was not prescribed.

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess prescribers' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS educational materials, enrollment form, and Prescribing Information (PI) of each product. This protocol will describe the administration of the surveys that will be conducted among prescribers who are enrolled in the TIRF REMS Access Program. Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

3. OBJECTIVES OF THE EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of prescribers around the following key information and risk messages communicated through the REMS:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.

2. TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 or older for Actiq® and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

3. TIRF medicines contain fentanyl, an opioid agonist and a Schedule II-controlled substance, with abuse liability similar to other opioid analgesics.

4. TIRF medicines are not interchangeable with each other, regardless of route of administration.

5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey will also collect data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC) and will be administered by UBC.

4.1 Survey Design

This survey will be conducted among a sample of prescribers who are enrolled in the TIRF REMS Access Program. Respondents who participate in the previous wave of the TIRF survey will not be eligible to participate in subsequent survey waves.

The survey will be administered using the following modalities:

- Self-administered, online through a secure website

- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

The survey included in Appendix A is written to reflect wording for both methods of survey administration: Internet-based and telephone.

All respondents who complete the survey and who provide their contact information will be mailed a $125 honorarium for their time.

4.1.1 Qualitative Research on the Survey

The FDA provided feedback to the TRIG on the Knowledge, Attitudes and Behaviors (KAB) survey results for prescribers included in the 12-month REMS Assessment results. The FDA requested that the TRIG investigate the causes for low correct response rates to specific questions in the survey by conducting research to determine the reasons for the poor performance on these questions, and to assess proposed revised wording to select questions. Qualitative research was performed in 2013 prior to Wave 2 of the survey. Findings were incorporated into the survey and results from the revised survey were included in the 24-month REMS Assessment Report,

4.1.2 Questions on REMS Goals

The KAB questionnaire is made up of multiple-choice, close-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and one open-ended question. These will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3.

Questions will be presented in several formats:

- Statements or questions asking the respondent to indicate whether a statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use “yes” or “no” as potential response options);

- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and

- One question allowing for the respondent to list questions about the products or comments.

Questionnaires will be analyzed to determine prescriber understanding of each key risk message.

For statements or questions that use “true” or “yes” vs. “false” or “no” response options, the desired response for key risk messages is generally “true” or “yes” indicating knowledge of,

or behavior in accordance with, the objectives of the REMS. However, some questions are formatted to have the respondent disagree with the statement as written by providing response options of "false" or "no" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired response**
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a	Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	**TRUE**
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before	**FALSE**
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	**FALSE**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**TRUE**
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	**TRUE**
7c	TIRF medicines may be used to treat opioid non-tolerant patients.	**FALSE**
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	**TRUE**

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.		
Question No.	**Question**	**Desired response**
9	In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a	Acute or postoperative pain	**NO**

9b	Headache or migraine pain	**NO**
9c	Dental pain	**NO**
9d	Breakthrough pain from cancer	**YES**
9e	Chronic non-cancer pain	**NO**
13	The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.	**13b.** Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.

Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II-controlled substance, with abuse liability similar to other opioid analgesics.		
Question No.	**Question**	**Desired response**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**TRUE**
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a	A personal history of psychiatric illness	**YES**
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**YES**
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10a	TIRF medicines can be abused in a manner similar to other opioid agonists.	**TRUE**

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired response**
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10b	TIRF medicines are interchangeable with each other regardless of route of administration.	**FALSE**
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in	**TRUE**

	the pharmacokinetics of fentanyl absorption.	
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**TRUE**
14	A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.	**14b.** The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.

4.1.3 Additional Questions

The survey includes questions about the requirements of the TIRF REMS Access Program and receipt and understanding of the TIRF educational materials and the Patient-Prescriber Agreement Form. The following question about behaviors will be asked after the key risk message questions:

Question 12: How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.
Ask patients (or their caregivers) about the presence of children in the home
Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
Give patients (or their caregivers) the Medication Guide for their TIRF medicine

Demographic information will be collected at the end of the survey.

4.2 Participant Recruitment

A random sample of prescribers who are enrolled in the TIRF REMS Access Program will be invited to participate via an invitation letter. The text of the sample written invitation to prescribers can be found in Appendix B. If the required number of completed surveys is not achieved within the expected timeframe of approximately one to two weeks after the first mailing, reminder letters will be sent to non-responders from the original sample with subsequent fax, e-mail, or United States (US) Mail follow-up to maximize participation. The distribution within the mailing to the second sample will be adjusted in accordance with the allocation in the original sample. If these efforts do not result in the required number of

surveys within two to three weeks, then a new sample of prescribers will be randomly selected.

All respondents who complete the survey and who provide their contact information will be mailed a $125 honorarium to thank them for their participation. Prescribers who practice in Vermont, Massachusetts, or Minnesota and complete the survey will not receive compensation. Participants will be informed that prescribers from these states are eligible to participate, but they will not receive compensation for their participation. The mailing will also include a Thank You Letter, a copy of the Important Safety Information (ISI), and a copy of the correct answers to key risk message questions.

4.2.1 Measures to Minimize Bias in the Sample

The sample of prescribers who are invited to participate will be a random sample of all enrolled prescribers. The sample of participating prescribers will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of prescribers for participation.

Prescribers will be offered online or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the online survey or when calling the Survey Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

5. STUDY POPULATION

5.1.1 Sample Size

A sample of 300 healthcare providers who are enrolled in the TIRF REMS Access Program is proposed for each survey wave. The size of the sample was determined based on both practical and statistical considerations. There is no target comprehension rate specified *a priori*. A sample of 300 completed surveys will allow estimation of the comprehension rate for each risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval

5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.2 Inclusion Criteria

All prescribers who are enrolled in the TIRF REMS Access Program are eligible to participate in this survey, with the exceptions noted below.

5.1.3 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Prescribers who have previously participated in the TIRF REMS KAB survey
- Prescribers or their immediate family members who have ever worked for ever worked for Anesta LLC; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc.; Par Pharmaceutical, Inc.; Teva Pharmaceuticals, Ltd.; UBC; McKesson Specialty Care Solutions; RelayHealth; or the FDA.

6. SURVEY PROCESS

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm prescriber eligibility. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, the respondent is immediately notified with a

"thank you" message that survey participation has ended. If eligible, the respondent is allowed to continue survey participation.

The data entry system used for both methods of survey administration has been validated and is secure for receiving and storing survey data. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Prescriber-identifying information will be stored separately from survey data.

6.1.1 Telephone

A trained interviewer from the Survey Coordinating Center will conduct the telephone interviews using a CATI program. The screening and main elements of the questionnaire will be administered sequentially during the same telephone call.

Telephone interviewing allows participation of prescribers who do not have Internet access. It will also be convenient for prescribers to participate since they can call in and be interviewed at their convenience during the specified time period when the Survey Coordinating Center is available.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If the prescriber selects to participate in the survey online, he/she will be directed to a secured website to complete screening questions. An Internet survey will be convenient for respondents to participate since they can complete the questionnaire at any time.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer the survey.

All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. The data from the sample population will be reported using frequency distributions of responses to all questions.

The following will be reported as part of this analysis:

- The number of invitations issued to prescribers
- The number of reminder letters
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents eligible for participation who complete the survey
- Representativeness of prescribers based on geography
- Description of survey participants, including:
  - Gender
  - Medical degree of respondent: MD, DO, NP, PA
  - Medical specialty
  - Years of professional experience
  - How many times per month TIRF medicines prescribed in the last 6 months
  - Geographic region of practice

Additional descriptive statistics may be reported as appropriate.

7.1.1 Analysis Population

The analysis population will be based on eligible prescribers who completed all questions presented to them in the survey ("completers").

7.1.2 Description of Primary Analyses

Primary analyses are done for all key risk messages using data from all completers. The primary analysis for a key risk message evaluates the rate for each correct response to each individual question/item defined by the key risk message. The specific correct response to each question/item is identified in the body of the risk message table.

7.1.3 Description of Secondary Analyses

Secondary analyses are done only for those key risk messages that contain multiple questions/items using data from all completers. The secondary analysis entails a frequency distribution of the number of respondents who got 0, 1, etc. correct responses across the total number of items for the given key risk message.

8. SAFETY EVENT REPORTING

The term 'Safety Event' is defined as any information reported by a survey respondent that meets the criteria of an adverse event or product complaint. While it is not the intention of the survey to solicit the report of information that meets the criteria of a Safety Event, it is possible that a respondent may spontaneously report information that meets this criteria in free text fields of the survey (Internet-based administration) or while in conversation with the Survey Coordinating Center (telephone-based administration). The Internet-based questionnaires will be monitored for any comments recorded in the free text fields. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. Respondents will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact them if there are questions about the survey. Information on all reports (Internet or telephone) that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE PSP.

9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The electronic data capture (EDC) system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail the $125 honorarium, a Thank You Letter, the correct responses to key risk messages, and the ISI after the survey is completed. Respondent contact information is also requested when necessary to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions in addition to instances where a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information (see Section 8 above).

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to prescribe TIRF medicines.

Appendix A Prescriber Questionnaire

Survey Legend

- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.

- **(INTERVIEWER)** is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by telephone only (for example, spontaneous adverse event reporting).

- **[ONLINE]** indicates a question is worded specifically for administering the survey online. **[PHONE]** indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.

- **[BEGIN ONLINE/PHONE SURVEY CONTENT]** and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.

- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

  Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.

- **[RANDOMIZE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as “I don’t know,” “Prefer not to answer” or “None of the above” will always appear at the end of the randomized responses.

- **[GO TO Qx]** (skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

- **[FREE TEXT]** indicates to the programmer that one line should be provided for data entry.

- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines).

Survey Legend

- **[DROP-DOWN LIST INPUT WITH STATES TABLE]** indicates to the programmer that the response should be a drop-down list containing the states and US territories in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

- The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

Northeast Region

– New England Division - ME, NH, VT, MA, RI, CT
– Middle Atlantic Division - NY, NJ, PA

Midwest Region

– East North Central Division - OH, IN, IL, MI, WI
– West North Central Division - MN, IA, MO, ND, SD, NE, KS

South Region

– South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
– East South Central Division - KY, TN, AL, MS
– West South Central Division - AR, LA, OK, TX

Survey Legend

West

- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV
- Pacific Division WA, OR, CA, AK, HI

- The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

[BEGIN SURVEY CONTENT]

[ONLINE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess prescribers' understanding of the safe use and prescribing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc. The survey will take approximately 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to prescribe TIRF medicines.

How We Use Your Information

Your answers to the survey questions will be combined with answers given by other healthcare professionals taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $125 honorarium for your time and participation. This compensation represents the fair value for your services in connection with completion of the survey. The amount of the compensation was not determined in any manner that takes into account the volume or value of any referrals or business otherwise generated by you.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions. Physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your personal

information will not be used in a manner inconsistent with this document. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

How to Learn More about This Survey

If you have questions about the survey, or problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Be sure to write down this telephone number; it will not be displayed again.

Taking the Survey

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

[PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess prescribers' understanding of the safe use and prescribing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." **(INTERVIEWER: Say "TIRF" then spell out T-I-R-F)** The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.);Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc; and Par Pharmaceutical, Inc. The survey will take approximately 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to prescribe TIRF medicines.

Now I would like to read some information about how your contact information will be used.

Your answers to the survey questions will be combined with answers given by other healthcare professionals taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $125 honorarium for your time and participation. This compensation represents the fair value for your services in connection with completion of the survey. The amount of the compensation was not determined in any manner that takes into account the volume or value of any referrals or business otherwise generated by you.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions. Physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

Now I would like to tell you some information about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your personal

information will not be used in a manner inconsistent with this document. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

Now I will tell you how you can learn more about this survey. Please have a pen or pencil ready to write down a telephone number you can call if you have any questions about the survey. If you have questions about the survey, please ask me at any time. If you have questions at a later time, please contact the Survey Coordinating Center at 1-877-379-3297. Please feel free to ask me to repeat any questions or statements as we go through the survey. Once you have answered a question and moved on, we cannot go back and change your answers. Thank you for your participation in this survey.

[END PHONE PREAMBLE 1]

[BEGIN INCLUSION/EXCLUSION QUESTIONS]

1. Your agreement to participate in this survey confirms mutual understanding in connection with completion of the survey and the fair market value of the payment to be rendered in connection with those services.

   Do you agree to participate in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

   - ○ Yes **[TERMINATE]**
   - ○ No
   - ○ I don't know **[TERMINATE]**

3. Are you enrolled in the TIRF REMS Access Program?

   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

4. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

   - □ Anesta LLC **[TERMINATE]**
   - □ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**
   - □ Depomed, Inc. **[TERMINATE]**
   - □ Galena Biopharma, Inc. **[TERMINATE]**
   - □ Insys Therapeutics **[TERMINATE]**

- ☐ Mallinckrodt Pharmaceuticals **[TERMINATE]**
- ☐ McKesson Specialty Care Solutions **[TERMINATE]**
- ☐ Meda Pharmaceuticals **[TERMINATE]**
- ☐ Mylan, Inc. **[TERMINATE]**
- ☐ Par Pharmaceutical, Inc. **[TERMINATE]**
- ☐ RelayHealth **[TERMINATE]**
- ☐ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- ☐ United BioSource Corporation **[TERMINATE]**
- ☐ FDA **[TERMINATE]**
- ☐ None of these apply **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- ☐ I don't know **[TERMINATE]**
- ☐ Prefer not to answer **[TERMINATE]**

[END INCLUSION/EXCLUSION QUESTIONS]

5. Please select True, False, or I don't know for each of the following.

According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:

	[RANDOMIZE LIST]	True	False	I don't know
5a.	Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	○	○	○
5b.	Who are not currently taking opioid therapy, but have taken opioid therapy before	○	○	○
5c.	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	○	○	○

6. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
6a.	A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time.	○	○	○
6b.	A cancer patient who has been on an around-the-clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.	○	○	○

7. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
7a.	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	○	○	○
7b.	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	○	○	○
7c.	TIRF medicines may be used to treat opioid non-tolerant patients.	○	○	○
7d.	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	○	○	○
7e.	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	○	○	○

8. Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
8a.	A personal history of psychiatric illness	○	○	○
8b.	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	○	○	○
8c.	A family history of asthma	○	○	○

9. In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
9a.	Acute or postoperative pain	○	○	○
9b.	Headache or migraine pain	○	○	○
9c.	Dental pain	○	○	○
9d.	Breakthrough pain from cancer	○	○	○
9e.	Chronic non-cancer pain	○	○	○

10. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
10a.	TIRF medicines can be abused in a manner similar to other opioid agonists.	○	○	○
10b.	TIRF medicines are interchangeable with each other regardless of route of administration.	○	○	○
10c.	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	○	○	○
10d.	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	○	○	○

11. Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:

	[RANDOMIZE LIST]	True	False	I don't know
11a.	8 mg oral hydromorphone/day	○	○	○
11b.	60 mg oral morphine/day	○	○	○
11c.	30 mg oral oxycodone/day	○	○	○
11d.	25 mcg transdermal fentanyl/hour	○	○	○
11e.	25 mg oral oxymorphone/day	○	○	○
11f.	An equianalgesic dose of another oral opioid	○	○	○

12. How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.

	[RANDOMIZE LIST]	Always	Only with the first prescription	Sometimes	Never	I don't know
12a.	Ask patients (or their caregivers) about the presence of children in the home	○	○	○	○	○
12b.	Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	○	○	○	○	○
12c.	Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	○	○	○	○	○
12d.	Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	○	○	○	○	○
12e.	Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	○	○	○	○	○
12f.	Give patients (or their caregivers) the Medication Guide for their TIRF medicine	○	○	○	○	○

13. The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine?

[RANDOMIZE LIST]

13a. ○ Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.

13b. ○ Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.

13c. ○ Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.

13d. ○ Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.

13e. ○ I don't know

14. A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.

[RANDOMIZE LIST]

14a. ○ The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.

14b. ○ The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.

14c. ○ Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.

14d. ○ The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.

14e. ○ I don't know.

15. A patient is starting titration with a TIRF medicine. What dose must they start with? Please select one option.

[RANDOMIZE LIST]

15a. ○ An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.

15b. ○ The dose that the prescriber believes is appropriate based on their clinical experience.

15c. ○ The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.

15d. ○ The median available dose.

15e. ○ I don't know.

16. A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do? Please pick the best option of the scenarios described.

[RANDOMIZE LIST]

16a. ○ Take another (identical) dose of the TIRF medicine immediately.

16b. ○ Take a dose of an alternative rescue medicine.

16c. ○ Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.

16d. ○ Double the dose and take immediately.

16e. ○ I don't know.

17. A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please pick the best option of the scenarios described.

[RANDOMIZE LIST]

17a. ○ The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.

17b. ○ Use of a TIRF medicine with a CYP3A4 inhibitor may require a dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.

17c. ○ There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.

17d. ○ The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

17e. ○ I don't know.

18. Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
18a.	TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.	○	○	○
18b.	Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.	○	○	○
18c.	Instruct patients that, if they stop taking their around-the-clock opioid medicine, they can continue to take their TIRF medicine.	○	○	○
18d.	Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.	○	○	○

19. Can patients continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine?

- ○ Yes
- ○ No
- ○ I don't know

[PREAMBLE 2]

The next set of questions is about the educational materials for TIRF medicines and the TIRF Patient-Prescriber Agreement. As a reminder, the TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and generic versions of any of these brands.

20. Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you prescribe?

- ○ Yes
- ○ No **[GO TO Q22]**
- ○ I don't know **[GO TO Q22]**

21. Did you read the Full Prescribing Information for the TIRF medicine(s) that you prescribe?

- ○ Yes
- ○ No
- ○ I don't know

22. Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you prescribe?

- ○ Yes
- ○ No **[GO TO Q24]**
- ○ I don't know **[GO TO Q24]**

23. Did you read the Medication Guide for the TIRF medicine(s) that you prescribe?

- ○ Yes
- ○ No
- ○ I don't know

24. Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?

- ○ Yes
- ○ No **[GO TO Q26]**
- ○ I don't know **[GO TO Q26]**

25. What are your questions? **[MULTILINE INPUT]**

26. Do you review the Patient-Prescriber Agreement Form with each of your patients for whom you prescribe TIRF medicines or their caregiver?

- ○ Yes
- ○ No **[GO TO Q28]**
- ○ I don't know **[GO TO Q28]**

27. Do you and the patient or their caregiver sign the Patient-Prescriber Agreement Form for TIRF medicines after you have reviewed it with him/her?

- ○ Yes
- ○ No
- ○ I don't know

28. Do you give a copy of the Patient-Prescriber Agreement Form for TIRF medicines to the patient or their caregiver?

- ○ Yes
- ○ No
- ○ I don't know

[DEMOGRAPHICS PREAMBLE 1]

There are just a few more questions to help us combine your answers with other answers we have received.

29. On average, how many times per month have you prescribed the TIRF medicines within the last 6 months?

- ○ None **[GO TO DEMOGRAPHICS PREAMBLE 2]**
- ○ 1 – 2 times per month
- ○ 3 – 5 times per month
- ○ More than 5 times per month
- ○ I don't remember

30. Please select the TIRF medicines that you have prescribed within the last 6 months. Please select all that apply.

- ☐ Abstral®
- ☐ Actiq® or generic Actiq®
- ☐ Fentora®
- ☐ Lazanda®
- ☐ Onsolis®
- ☐ Subsys®

[DEMOGRAPHICS PREAMBLE 2]

These last few questions are for demographic purposes.

31. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

32. What is your medical degree?

- ○ MD
- ○ DO
- ○ Nurse Practitioner
- ○ Physician Assistant
- ○ Prefer not to answer

33. In total, how many years have you been practicing medicine, since completing your education?

- ○ Less than 3 years
- ○ 3 – 5 years
- ○ 6 – 10 years
- ○ 11 – 15 years
- ○ More than 15 years
- ○ Prefer not to answer

34. In which state do you practice?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" at END]

35. What is your medical specialty?

- ○ Oncology
- ○ Primary care
- ○ Pain management
- ○ Other (please specify): **[FREE TEXT]**
- ○ No designated specialty

[PHONE ONLY: BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- ○ Yes
- ○ No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[CLOSING 1]

We would like to send you a $125 honorarium within the next few weeks to thank you for your time, but we need your name and address to do so. If you do not provide your name and address you will not receive the honorarium for your time and participation in the survey. As a reminder, physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion.

Do you agree to give us your name and mailing address so we can send you the honorarium?

○ Yes

○ No **[SKIP TO CLOSING 2]**

FIRST NAME: **[FREE TEXT]**

LAST NAME: **[FREE TEXT]**

ADDRESS: **[MULTILINE INPUT]**

CITY: **[FREE TEXT]**

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: **[5 NUMERIC CHARACTERS ONLY]**

[CLOSING 2]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

Do you want to provide your telephone number?

○ Yes

○ No **[SKIP TO CLOSING 3]**

Telephone: **[MUST BE 10-DIGIT NUMERIC CHARACTERS]**

[END CLOSING 2]

[CLOSING 3]

That ends the survey. Thank you again for your help.

[END OF SURVEY CONTENT]

Appendix B SAMPLE Prescriber Invitation Letter

[CURR_DATE]

[PRESCRIBER NAME]

[STREET_ADDR]

[CITY], [STATE] [ZIP]

Dear [PRESCRIBER NAME]:

You were selected to receive this letter because you have enrolled in the TIRF REMS Access Program. We are contacting you to invite you to participate in a survey being conducted by the manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines, as required by the Food and Drug Administration (FDA). The purpose of the survey is to assess prescribers' understanding of the safe and appropriate use of these medicines. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

The manufacturers of TIRF medicines (collectively referred to as the "TIRF REMS Industry Group") include Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc., and Par Pharmaceutical, Inc. These manufacturers are looking for 300 prescribers to complete the survey. Eligible prescribers who complete the survey will be sent a $125 honorarium to thank them for their time. The survey will take 15-20 minutes.

Your answers will be kept strictly confidential and will be combined with the answers from other prescribers who take this survey. Your name will not be used in the report of this survey and your contact information will only be used to send you a $125 honorarium for the time you took to complete the survey and if required to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions. Prescribers who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

You are under no obligation to participate in this survey. If you are interested in participating, go to **www.XXXXXXXXXX.com** anytime or call **1-877-379-3297,** 8AM to 8PM Eastern Time Monday through Friday. You will be asked to give this unique code prior to starting the survey: **[CODE_ID]**.

* We recommend that you take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.

Please have this letter with you at the time you take the survey. Thank you in advance for your help with this important effort.

Sincerely,

The TIRF REMS Survey Team

1-877-379-3297
www.TIRFREMSsurvey.com

Appendix B Prescriber Survey Listings and Sub-group Analysis Tables

TABLE 6.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 20, 21, 22, AND 23):

- **S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.**
- **S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 23).**

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=33	
	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:				
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer				
True [1]	241	90.3 (86.1, 93.5)	29	87.9 (71.8, 96.6)
False	19	7.1	3	9.1
I don't know	7	2.6	1	3.0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before				
False [1]	234	87.6 (83.1, 91.3)	27	81.8 (64.5, 93.0)
True	19	7.1	5	15.2
I don't know	14	5.2	1	3.0

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=33	
	N	% (95% CI)	N	% (95% CI)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy				
False [1]	231	86.5 (81.8, 90.4)	28	84.8 (68.1, 94.9)
True	26	9.7	2	6.1
I don't know	10	3.7	3	9.1
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.				
True [1]	233	87.3 (82.7, 91.0)	27	81.8 (64.5, 93.0)
False	27	10.1	5	15.2
I don't know	7	2.6	1	3.0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.				
True [1]	259	97.0 (94.2, 98.7)	28	84.8 (68.1, 94.9)
False	1	0.4	1	3.0
I don't know	7	2.6	4	12.1
7c: TIRF medicines may be used to treat opioid non-tolerant patients.				
False [1]	223	83.5 (78.5, 87.8)	23	69.7 (51.3, 84.4)
True	38	14.2	8	24.2
I don't know	6	2.2	2	6.1

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=33	
	N	% (95% CI)	N	% (95% CI)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.				
True [1]	230	86.1 (81.4, 90.1)	22	66.7 (48.2, 82.0)
False	31	11.6	11	33.3
I don't know	6	2.2	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 6.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 20, 21, 22, AND 23):

- **S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.**
- **S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 23).**

Demonstrated Understanding	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=33	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	1	0.4	0	0.0
2 correct responses	3	1.1	1	3.0
3 correct responses	6	2.2	2	6.1
4 correct responses	11	4.1	4	12.1
5 correct responses	35	13.1	4	12.1
6 correct responses	70	26.2	14	42.4
7 correct responses	141	52.8	8	24.2
Average number of correct responses	6.2 (5.9, 7.0) [1]		5.6 (4.9, 7.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 7.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 20, 21, 22, AND 23):

- **S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.**
- **S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 23).**

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=33	
	N	% (95% CI)	N	% (95% CI)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.				
9a: Acute or postoperative pain				
No [1]	237	88.8 (84.3, 92.3)	25	75.8 (57.7, 88.9)
Yes	29	10.9	8	24.2
I don't know	1	0.4	0	0.0

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=33	
	N	% (95% CI)	N	% (95% CI)
9b: Headache or migraine pain				
No [1]	240	89.9 (85.6, 93.2)	29	87.9 (71.8, 96.6)
Yes	27	10.1	4	12.1
I don't know	0	0.0	0	0.0
9c: Dental pain				
No [1]	260	97.4 (94.7, 98.9)	32	97.0 (84.2, 99.9)
Yes	7	2.6	1	3.0
I don't know	0	0.0	0	0.0
9d: Breakthrough pain from cancer				
Yes [1]	256	95.9 (92.7, 97.9)	32	97.0 (84.2, 99.9)
No	11	4.1	1	3.0
I don't know	0	0.0	0	0.0
9e: Chronic non-cancer pain				
No [1]	167	62.5 (56.4, 68.4)	19	57.6 (39.2, 74.5)
Yes	98	36.7	14	42.4
I don't know	2	0.7	0	0.0

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=33	
	N	% (95% CI)	N	% (95% CI)
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.				
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks. [1]	176	65.9 (59.9, 71.6)	23	69.7 (51.3, 84.4)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	28	10.5	2	6.1
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	17	6.4	2	6.1
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	19	7.1	3	9.1
I don't know	27	10.1	3	9.1

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 20, 21, 22, AND 23):

- **S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.**
- **S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 23).**

Demonstrated Understanding	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=33	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	3	1.1	0	0.0
2 correct responses	3	1.1	1	3.0
3 correct responses	18	6.7	2	6.1
4 correct responses	41	15.4	7	21.2
5 correct responses	103	38.6	14	42.4
6 correct responses	99	37.1	9	27.3
Average number of correct responses	5.0 (4.8, 6.0) [1]		4.8 (4.2, 6.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

Client: TRIG Project: TIRF Wave 3

Report Run Date and Time: 10/15/2014 1:50 PM

TABLE 8.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 20, 21, 22, AND 23):

- **S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.**
- **S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 23).**

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=33	
	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.				
True [1]	266	99.6 (97.9, 100.0)	33	100.0 (89.4, 100.0)
False	1	0.4	0	0.0
I don't know	0	0.0	0	0.0

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=33	
	N	% (95% CI)	N	% (95% CI)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.				
8a: A personal history of psychiatric illness				
Yes [1]	228	85.4 (80.6, 89.4)	24	72.7 (54.5, 86.7)
No	17	6.4	6	18.2
I don't know	22	8.2	3	9.1
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse				
Yes [1]	266	99.6 (97.9, 100.0)	33	100.0 (89.4, 100.0)
No	1	0.4	0	0.0
I don't know	0	0.0	0	0.0
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.				
True [1]	261	97.8 (95.2, 99.2)	31	93.9 (79.8, 99.3)
False	6	2.2	1	3.0
I don't know	0	0.0	1	3.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 20, 21, 22, AND 23):

- **S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.**
- **S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 23).**

Demonstrated Understanding	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=33	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0
2 correct responses	4	1.5	1	3.0
3 correct responses	39	14.6	9	27.3
4 correct responses	224	83.9	23	69.7
Average number of correct responses	3.8 (3.6, 4.0) [1]		3.7(3.1, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 20, 21, 22, AND 23):

- **S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.**
- **S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 23).**

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=33	
	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
10b: TIRF medicines are interchangeable with each other regardless of route of administration.				
False [1]	250	93.6 (90.0, 96.2)	29	87.9 (71.8, 96.6)
True	12	4.5	3	9.1
I don't know	5	1.9	1	3.0
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.				
True [1]	258	96.6 (93.7, 98.4)	32	97.0 (84.2, 99.9)
False	5	1.9	1	3.0
I don't know	4	1.5	0	0.0

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=33	
	N	% (95% CI)	N	% (95% CI)
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.				
True [1]	246	92.1 (88.2, 95.1)	26	78.8 (61.1, 91.0)
False	13	4.9	5	15.2
I don't know	8	3.0	2	6.1
Question 14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.				
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose. [1]	202	75.7 (70.1, 80.7)	21	63.6 (45.1, 79.6)
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	24	9.0	2	6.1
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	1	0.4	2	6.1
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	26	9.7	6	18.2
I don't know.	14	5.2	2	6.1

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 9.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 20, 21, 22, AND 23):

- **S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.**
- **S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 23).**

Demonstrated Understanding	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=33	
	N	%	N	%
0 correct responses	2	0.7	0	0.0
1 correct response	5	1.9	2	6.1
2 correct responses	14	5.2	4	12.1
3 correct responses	61	22.8	10	30.3
4 correct responses	185	69.3	17	51.5
Average number of correct responses	3.6 (3.4, 4.0) [1]		3.3 (2.8, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 6.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 2: MEDICAL DEGREE OF RESPONDENTS (QUESTION 32):

- **S-2a - MD**
- **S-2b - DO**
- **S-2c - Nurse Practitioner**
- **S-2d - Physician Assistant**

Question	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:								
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer								
True [1]	166	89.2 (83.9, 93.3)	20	87.0 (66.4, 97.2)	50	94.3 (84.3, 98.8)	33	91.7 (77.5, 98.2)
False	14	7.5	2	8.7	2	3.8	3	8.3
I don't know	6	3.2	1	4.3	1	1.9	0	0.0

Question	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before								
False [1]	158	84.9 (79.0, 89.8)	20	87.0 (66.4, 97.2)	47	88.7 (77.0, 95.7)	34	94.4 (81.3, 99.3)
True	18	9.7	2	8.7	4	7.5	0	0.0
I don't know	10	5.4	1	4.3	2	3.8	2	5.6
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy								
False [1]	161	86.6 (80.8, 91.1)	18	78.3 (56.3, 92.5)	47	88.7 (77.0, 95.7)	32	88.9 (73.9, 96.9)
True	18	9.7	5	21.7	2	3.8	3	8.3
I don't know	7	3.8	0	0.0	4	7.5	1	2.8
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.								
True [1]	161	86.6 (80.8, 91.1)	21	91.3 (72.0, 98.9)	48	90.6 (79.3, 96.9)	28	77.8 (60.8, 89.9)
False	20	10.8	2	8.7	3	5.7	7	19.4
I don't know	5	2.7	0	0.0	2	3.8	1	2.8

Question	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.								
True [1]	181	97.3 (93.8, 99.1)	22	95.7 (78.1, 99.9)	47	88.7 (77.0, 95.7)	35	97.2 (85.5, 99.9)
False	1	0.5	0	0.0	1	1.9	0	0.0
I don't know	4	2.2	1	4.3	5	9.4	1	2.8
7c: TIRF medicines may be used to treat opioid non-tolerant patients.								
False [1]	155	83.3 (77.2, 88.4)	19	82.6 (61.2, 95.0)	43	81.1 (68.0, 90.6)	28	77.8 (60.8, 89.9)
True	29	15.6	3	13.0	6	11.3	8	22.2
I don't know	2	1.1	1	4.3	4	7.5	0	0.0
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.								
True [1]	154	82.8 (76.6, 87.9)	18	78.3 (56.3, 92.5)	46	86.8 (74.7, 94.5)	32	88.9 (73.9, 96.9)
False	28	15.1	5	21.7	7	13.2	2	5.6
I don't know	4	2.2	0	0.0	0	0.0	2	5.6

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 6.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 2: MEDICAL DEGREE OF RESPONDENTS (QUESTION 32):

- **S-2a - MD**
- **S-2b - DO**
- **S-2c - Nurse Practitioner**
- **S-2d - Physician Assistant**

Demonstrated Understanding	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	1	1.9	0	0.0
2 correct responses	4	2.2	0	0.0	0	0.0	0	0.0
3 correct responses	4	2.2	2	8.7	1	1.9	1	2.8
4 correct responses	11	5.9	1	4.3	2	3.8	1	2.8
5 correct responses	23	12.4	4	17.4	5	9.4	6	16.7
6 correct responses	51	27.4	4	17.4	17	32.1	11	30.6
7 correct responses	93	50.0	12	52.2	27	50.9	17	47.2
Average number of correct responses	6.1 (5.8, 7.0) [1]		6.0 (5.2, 7.0) [1]		6.2 (5.6, 7.0) [1]		6.2 (5.5, 7.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 7.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 2: MEDICAL DEGREE OF RESPONDENTS (QUESTION 32):

- **S-2a - MD**
- **S-2b - DO**
- **S-2c - Nurse Practitioner**
- **S-2d - Physician Assistant**

Question	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.								
9a: Acute or postoperative pain								
No [1]	162	87.1 (81.4, 91.6)	20	87.0 (66.4, 97.2)	47	88.7 (77.0, 95.7)	31	86.1 (70.5, 95.3)
Yes	24	12.9	3	13.0	6	11.3	4	11.1
I don't know	0	0.0	0	0.0	0	0.0	1	2.8

Question	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9b: Headache or migraine pain								
No [1]	162	87.1 (81.4, 91.6)	20	87.0 (66.4, 97.2)	51	96.2 (87.0, 99.5)	35	97.2 (85.5, 99.9)
Yes	24	12.9	3	13.0	2	3.8	1	2.8
I don't know	0	0.0	0	0.0	0	0.0	0	0.0
9c: Dental pain								
No [1]	178	95.7 (91.7, 98.1)	23	100.0 (85.2, 100.0)	53	100.0 (93.3, 100.0)	36	100.0 (90.3, 100.0)
Yes	8	4.3	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0	0	0.0
9d: Breakthrough pain from cancer								
Yes [1]	178	95.7 (91.7, 98.1)	21	91.3 (72.0, 98.9)	52	98.1 (89.9, 100.0)	35	97.2 (85.5, 99.9)
No	8	4.3	2	8.7	1	1.9	1	2.8
I don't know	0	0.0	0	0.0	0	0.0	0	0.0
9e: Chronic non-cancer pain								

Question	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
No [1]	115	61.8 (54.4, 68.8)	12	52.2 (30.6, 73.2)	35	66.0 (51.7, 78.5)	23	63.9 (46.2, 79.2)
Yes	69	37.1	11	47.8	18	34.0	13	36.1
I don't know	2	1.1	0	0.0	0	0.0	0	0.0
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.								
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks. [1]	129	69.4 (62.2, 75.9)	13	56.5 (34.5, 76.8)	35	66.0 (51.7, 78.5)	21	58.3 (40.8, 74.5)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	13	7.0	4	17.4	7	13.2	5	13.9

Question	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	13	7.0	0	0.0	3	5.7	3	8.3
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	11	5.9	1	4.3	5	9.4	5	13.9
I don't know	20	10.8	5	21.7	3	5.7	2	5.6

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 2: MEDICAL DEGREE OF RESPONDENTS (QUESTION 32):

- **S-2a - MD**
- **S-2b - DO**
- **S-2c - Nurse Practitioner**
- **S-2d - Physician Assistant**

Demonstrated Understanding	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	3	1.6	0	0.0	0	0.0	0	0.0
2 correct responses	3	1.6	1	4.3	0	0.0	0	0.0
3 correct responses	12	6.5	3	13.0	2	3.8	2	5.6
4 correct responses	29	15.6	4	17.4	8	15.1	7	19.4
5 correct responses	71	38.2	8	34.8	23	43.4	15	41.7
6 correct responses	68	36.6	7	30.4	20	37.7	12	33.3

Demonstrated Understanding	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	%	N	%	N	%	N	%
Average number of correct responses	5.0 (4.7, 6.0) [1]		4.7 (4.0, 6.0) [1]		5.2 (4.6, 6.0) [1]		5.0 (4.4, 6.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 2: MEDICAL DEGREE OF RESPONDENTS (QUESTION 32):

- **S-2a - MD**
- **S-2b - DO**
- **S-2c - Nurse Practitioner**
- **S-2d - Physician Assistant**

Question	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.								
True [1]	185	99.5 (97.0, 100.0)	23	100.0 (85.2, 100.0)	53	100.0 (93.3, 100.0)	36	100.0 (90.3, 100.0)
False	1	0.5	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0	0	0.0

Question	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.								
8a: A personal history of psychiatric illness								
Yes [1]	164	88.2 (82.6, 92.4)	16	69.6 (47.1, 86.8)	41	77.4 (63.8, 87.7)	29	80.6 (64.0, 91.8)
No	12	6.5	4	17.4	4	7.5	3	8.3
I don't know	10	5.4	3	13.0	8	15.1	4	11.1
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse								
Yes [1]	186	100.0 (98.0, 100.0)	22	95.7 (78.1, 99.9)	53	100.0 (93.3, 100.0)	36	100.0 (90.3, 100.0)
No	0	0.0	1	4.3	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0	0	0.0
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.								
True [1]	180	96.8 (93.1, 98.8)	23	100.0 (85.2, 100.0)	51	96.2 (87.0, 99.5)	36	100.0 (90.3, 100.0)
False	5	2.7	0	0.0	2	3.8	0	0.0
I don't know	1	0.5	0	0.0	0	0.0	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 2: MEDICAL DEGREE OF RESPONDENTS (QUESTION 32):

- **S-2a - MD**
- **S-2b - DO**
- **S-2c - Nurse Practitioner**
- **S-2d - Physician Assistant**

Demonstrated Understanding	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	0	0.0	0	0.0
2 correct responses	2	1.1	1	4.3	2	3.8	0	0.0
3 correct responses	25	13.4	6	26.1	10	18.9	7	19.4
4 correct responses	159	85.5	16	69.6	41	77.4	29	80.6
Average number of correct responses	3.8 (3.6, 4.0) [1]		3.7 (3.0, 4.0) [1]		3.7 (3.3, 4.0) [1]		3.8 (3.3, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

Client: TRIG Project: TIRF Wave 3

Report Run Date and Time: 10/28/2014 9:12 AM

TABLE 9.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 2: MEDICAL DEGREE OF RESPONDENTS (QUESTION 32):

- **S-2a - MD**
- **S-2b - DO**
- **S-2c - Nurse Practitioner**
- **S-2d - Physician Assistant**

Question	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
10b: TIRF medicines are interchangeable with each other regardless of route of administration.								
False [1]	169	90.9 (85.8, 94.6)	22	95.7 (78.1, 99.9)	51	96.2 (87.0, 99.5)	35	97.2 (85.5, 99.9)
True	11	5.9	1	4.3	2	3.8	1	2.8
I don't know	6	3.2	0	0.0	0	0.0	0	0.0

Question	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.								
True [1]	179	96.2 (92.4, 98.5)	23	100.0 (85.2, 100.0)	50	94.3 (84.3, 98.8)	36	100.0 (90.3, 100.0)
False	3	1.6	0	0.0	3	5.7	0	0.0
I don't know	4	2.2	0	0.0	0	0.0	0	0.0
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.								
True [1]	167	89.8 (84.5, 93.7)	23	100.0 (85.2, 100.0)	47	88.7 (77.0, 95.7)	34	94.4 (81.3, 99.3)
False	11	5.9	0	0.0	5	9.4	1	2.8
I don't know	8	4.3	0	0.0	1	1.9	1	2.8

Question	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.								
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose. [1]	137	73.7 (66.7, 79.8)	17	73.9 (51.6, 89.8)	40	75.5 (61.7, 86.2)	28	77.8 (60.8, 89.9)
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	16	8.6	4	17.4	5	9.4	0	0.0
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	2	1.1	0	0.0	0	0.0	1	2.8

Question	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	21	11.3	1	4.3	5	9.4	5	13.9
I don't know.	10	5.4	1	4.3	3	5.7	2	5.6

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 9.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 2: MEDICAL DEGREE OF RESPONDENTS (QUESTION 32):

- **S-2a - MD**
- **S-2b - DO**
- **S-2c - Nurse Practitioner**
- **S-2d - Physician Assistant**

Demonstrated Understanding	S-2a MD N=186		S-2b DO N=23		S-2c Nurse Practitioner N=53		S-2d Physician Assistant N=36	
	N	%	N	%	N	%	N	%
0 correct responses	2	1.1	0	0.0	0	0.0	0	0.0
1 correct response	4	2.2	0	0.0	2	3.8	1	2.8
2 correct responses	14	7.5	0	0.0	2	3.8	1	2.8
3 correct responses	44	23.7	7	30.4	14	26.4	6	16.7
4 correct responses	122	65.6	16	69.6	35	66.0	28	77.8
Average number of correct responses	3.5 (3.3, 4.0) [1]		3.7 (3.0, 4.0) [1]		3.5 (3.1, 4.0) [1]		3.7 (3.2, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 6.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – INTERNET:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=173		S-3c ≥ 20 min N=59	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:						
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer						
True [1]	42	84.0 (70.9, 92.8)	159	91.9 (86.8, 95.5)	55	93.2 (83.5, 98.1)
False	8	16.0	8	4.6	4	6.8
I don't know	0	0.0	6	3.5	0	0.0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before						
False [1]	45	90.0 (78.2, 96.7)	152	87.9 (82.0, 92.3)	53	89.8 (79.2, 96.2)
True	4	8.0	11	6.4	2	3.4
I don't know	1	2.0	10	5.8	4	6.8

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=173		S-3c ≥ 20 min N=59	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy						
False [1]	45	90.0 (78.2, 96.7)	154	89.0 (83.4, 93.3)	50	84.7 (73.0, 92.8)
True	4	8.0	9	5.2	8	13.6
I don't know	1	2.0	10	5.8	1	1.7
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.						
True [1]	40	80.0 (66.3, 90.0)	152	87.9 (82.0, 92.3)	51	86.4 (75.0, 94.0)
False	7	14.0	16	9.2	8	13.6
I don't know	3	6.0	5	2.9	0	0.0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.						
True [1]	48	96.0 (86.3, 99.5)	167	96.5 (92.6, 98.7)	54	91.5 (81.3, 97.2)
False	0	0.0	0	0.0	2	3.4
I don't know	2	4.0	6	3.5	3	5.1
7c: TIRF medicines may be used to treat opioid non-tolerant patients.						
False [1]	41	82.0 (68.6, 91.4)	141	81.5 (74.9, 87.0)	48	81.4 (69.1, 90.3)
True	8	16.0	26	15.0	10	16.9
I don't know	1	2.0	6	3.5	1	1.7

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=173		S-3c ≥ 20 min N=59	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.						
True [1]	41	82.0 (68.6, 91.4)	149	86.1 (80.1, 90.9)	47	79.7 (67.2, 89.0)
False	8	16.0	20	11.6	11	18.6
I don't know	1	2.0	4	2.3	1	1.7

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 6.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – INTERNET:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Demonstrated Understanding	S-3a <10 min N=50		S-3b 10 to <20 min N=173		S-3c ≥ 20 min N=59	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	1	0.6	0	0.0
2 correct responses	0	0.0	3	1.7	1	1.7
3 correct responses	3	6.0	1	0.6	2	3.4
4 correct responses	2	4.0	7	4.0	3	5.1
5 correct responses	8	16.0	22	12.7	7	11.9
6 correct responses	14	28.0	47	27.2	19	32.2
7 correct responses	23	46.0	92	53.2	27	45.8
Average number of correct responses	6.0 (5.5, 7.0) [1]		6.2 (5.9, 7.0) [1]		6.1 (5.5, 7.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

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Client: TRIG Project: TIRF Wave 3

Report Run Date and Time: 10/16/2014 2:23 PM

TABLE 7.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – INTERNET:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=173		S-3c ≥ 20 min N=59	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.						
9a: Acute or postoperative pain						
No [1]	46	92.0 (80.8, 97.8)	151	87.3 (81.4, 91.9)	49	83.1 (71.0, 91.6)
Yes	4	8.0	21	12.1	10	16.9
I don't know	0	0.0	1	0.6	0	0.0
9b: Headache or migraine pain						
No [1]	44	88.0 (75.7, 95.5)	154	89.0 (83.4, 93.3)	55	93.2 (83.5, 98.1)
Yes	6	12.0	19	11.0	4	6.8
I don't know	0	0.0	0	0.0	0	0.0

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=173		S-3c ≥ 20 min N=59	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9c: Dental pain						
No [1]	49	98.0 (89.4, 99.9)	169	97.7 (94.2, 99.4)	58	98.3 (90.9, 100.0)
Yes	1	2.0	4	2.3	1	1.7
I don't know	0	0.0	0	0.0	0	0.0
9d: Breakthrough pain from cancer						
Yes [1]	48	96.0 (86.3, 99.5)	167	96.5 (92.6, 98.7)	55	93.2 (83.5, 98.1)
No	2	4.0	6	3.5	4	6.8
I don't know	0	0.0	0	0.0	0	0.0
9e: Chronic non-cancer pain						
No [1]	35	70.0 (55.4, 82.1)	107	61.8 (54.2, 69.1)	36	61.0 (47.4, 73.5)
Yes	14	28.0	65	37.6	23	39.0
I don't know	1	2.0	1	0.6	0	0.0

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=173		S-3c ≥ 20 min N=59	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.						
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks. [1]	26	52.0 (37.4, 66.3)	116	67.1 (59.5, 74.0)	45	76.3 (63.4, 86.4)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	6	12.0	17	9.8	5	8.5
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	7	14.0	7	4.0	4	6.8
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	4	8.0	15	8.7	2	3.4
I don't know	7	14.0	18	10.4	3	5.1

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – INTERNET:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Demonstrated Understanding	S-3a <10 min N=50		S-3b 10 to <20 min N=173		S-3c ≥ 20 min N=59	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	1	2.0	2	1.2	0	0.0
2 correct responses	0	0.0	2	1.2	1	1.7
3 correct responses	4	8.0	11	6.4	4	6.8
4 correct responses	7	14.0	28	16.2	10	16.9
5 correct responses	21	42.0	67	38.7	20	33.9
6 correct responses	17	34.0	63	36.4	24	40.7

Demonstrated Understanding	S-3a <10 min N=50		S-3b 10 to <20 min N=173		S-3c ≥ 20 min N=59	
	N	%	N	%	N	%
Average number of correct responses	5.0 (4.4, 6.0) [1]		5.0 (4.7, 6.0) [1]		5.1 (4.6, 6.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – INTERNET:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=173		S-3c ≥ 20 min N=59	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.						
True [1]	49	98.0 (89.4, 99.9)	173	100.0 (97.9, 100.0)	59	100.0 (93.9, 100.0)
False	1	2.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.						
8a: A personal history of psychiatric illness						
Yes [1]	42	84.0 (70.9, 92.8)	152	87.9 (82.0, 92.3)	47	79.7 (67.2, 89.0)
No	3	6.0	11	6.4	6	10.2
I don't know	5	10.0	10	5.8	6	10.2

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=173		S-3c ≥ 20 min N=59	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse						
Yes [1]	50	100.0 (92.9, 100.0)	173	100.0 (97.9, 100.0)	59	100.0 (93.9, 100.0)
No	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.						
True [1]	47	94.0 (83.5, 98.7)	171	98.8 (95.9, 99.9)	56	94.9 (85.9, 98.9)
False	3	6.0	2	1.2	2	3.4
I don't know	0	0.0	0	0.0	1	1.7

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – INTERNET:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Demonstrated Understanding	S-3a <10 min N=50		S-3b 10 to <20 min N=173		S-3c ≥ 20 min N=59	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	0	0.0
2 correct responses	2	4.0	1	0.6	1	1.7
3 correct responses	8	16.0	21	12.1	13	22.0
4 correct responses	40	80.0	151	87.3	45	76.3
Average number of correct responses	3.8 (3.3, 4.0) [1]		3.9 (3.6, 4.0) [1]		3.7 (3.3, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – INTERNET:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=173		S-3c ≥ 20 min N=59	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
10b: TIRF medicines are interchangeable with each other regardless of route of administration.						
False [1]	46	92.0 (80.8, 97.8)	162	93.6 (88.9, 96.8)	54	91.5 (81.3, 97.2)
True	3	6.0	9	5.2	3	5.1
I don't know	1	2.0	2	1.2	2	3.4
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.						
True [1]	47	94.0 (83.5, 98.7)	170	98.3 (95.0, 99.6)	56	94.9 (85.9, 98.9)
False	2	4.0	1	0.6	3	5.1
I don't know	1	2.0	2	1.2	0	0.0

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=173		S-3c ≥ 20 min N=59	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.						
True [1]	43	86.0 (73.3, 94.2)	155	89.6 (84.1, 93.7)	57	96.6 (88.3, 99.6)
False	5	10.0	11	6.4	1	1.7
I don't know	2	4.0	7	4.0	1	1.7
Question 14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.						
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose. [1]	34	68.0 (53.3, 80.5)	131	75.7 (68.6, 81.9)	48	81.4 (69.1, 90.3)
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	2	4.0	14	8.1	5	8.5
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	0	0.0	2	1.2	0	0.0

Question	S-3a <10 min N=50		S-3b 10 to <20 min N=173		S-3c ≥ 20 min N=59	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	12	24.0	14	8.1	5	8.5
I don't know.	2	4.0	12	6.9	1	1.7

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 9.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – INTERNET:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Demonstrated Understanding	S-3a <10 min N=50		S-3b 10 to <20 min N=173		S-3c ≥ 20 min N=59	
	N	%	N	%	N	%
0 correct responses	0	0.0	1	0.6	1	1.7
1 correct response	3	6.0	2	1.2	1	1.7
2 correct responses	4	8.0	13	7.5	0	0.0
3 correct responses	13	26.0	38	22.0	14	23.7
4 correct responses	30	60.0	119	68.8	43	72.9
Average number of correct responses	3.4 (3.0, 4.0) [1]		3.6 (3.3, 4.0) [1]		3.6 (3.2, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 6.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY – TELEPHONE:

- **S-4a - <10 min**
- **S-4b – 10 to <20 min**
- **S-4c – ≥ 20 min**

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=3		S-4c ≥ 20 min N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:						
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer						
True [1]	0	-	3	100.0 (29.2, 100.0)	11	73.3 (44.9, 92.2)
False	0	-	0	0.0	2	13.3
I don't know	0	-	0	0.0	2	13.3
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before						
False [1]	0	-	1	33.3 (0.8, 90.6)	10	66.7 (38.4, 88.2)
True	0	-	2	66.7	5	33.3
I don't know	0	-	0	0.0	0	0.0

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=3		S-4c ≥ 20 min N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy						
False [1]	0	-	1	33.3 (0.8, 90.6)	9	60.0 (32.3, 83.7)
True	0	-	2	66.7	5	33.3
I don't know	0	-	0	0.0	1	6.7
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.						
True [1]	0	-	3	100.0 (29.2, 100.0)	14	93.3 (68.1, 99.8)
False	0	-	0	0.0	1	6.7
I don't know	0	-	0	0.0	0	0.0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.						
True [1]	0	-	3	100.0 (29.2, 100.0)	15	100.0 (78.2, 100.0)
False	0	-	0	0.0	0	0.0
I don't know	0	-	0	0.0	0	0.0
7c: TIRF medicines may be used to treat opioid non-tolerant patients.						
False [1]	0	-	1	33.3 (0.8, 90.6)	15	100.0 (78.2, 100.0)
True	0	-	2	66.7	0	0.0
I don't know	0	-	0	0.0	0	0.0

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=3		S-4c ≥ 20 min N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.						
True [1]	0	-	1	33.3 (0.8, 90.6)	14	93.3 (68.1, 99.8)
False	0	-	2	66.7	1	6.7
I don't know	0	-	0	0.0	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 6.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY – TELEPHONE:

- **S-4a - <10 min**
- **S-4b – 10 to <20 min**
- **S-4c – ≥ 20 min**

Demonstrated Understanding	S-4a <10 min N=0		S-4b 10 to <20 min N=3		S-4c >= 20 min N=15	
	N	%	N	%	N	%
0 correct responses	0	-	0	0.0	0	0.0
1 correct response	0	-	0	0.0	0	0.0
2 correct responses	0	-	0	0.0	0	0.0
3 correct responses	0	-	1	33.3	1	6.7
4 correct responses	0	-	1	33.3	2	13.3
5 correct responses	0	-	0	0.0	2	13.3
6 correct responses	0	-	1	33.3	3	20.0
7 correct responses	0	-	0	0.0	7	46.7
Average number of correct responses	-		4.3 (2.4, 7.0) [1]		5.9 (4.8, 7.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

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Client: TRIG Project: TIRF Wave 3

Report Run Date and Time: 10/16/2014 2:57 PM

TABLE 7.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY – TELEPHONE:

- **S-4a - <10 min**
- **S-4b – 10 to <20 min**
- **S-4c – ≥ 20 min**

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=3		S-4c ≥ 20 min N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.						
9a: Acute or postoperative pain						
No [1]	0	-	1	33.3 (0.8, 90.6)	15	100.0 (78.2, 100.0)
Yes	0	-	2	66.7	0	0.0
I don't know	0	-	0	0.0	0	0.0
9b: Headache or migraine pain						
No [1]	0	-	2	66.7 (9.4, 99.2)	14	93.3 (68.1, 99.8)
Yes	0	-	1	33.3	1	6.7
I don't know	0	-	0	0.0	0	0.0

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=3		S-4c ≥ 20 min N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9c: Dental pain						
No [1]	0	-	2	66.7 (9.4, 99.2)	14	93.3 (68.1, 99.8)
Yes	0	-	1	33.3	1	6.7
I don't know	0	-	0	0.0	0	0.0
9d: Breakthrough pain from cancer						
Yes [1]	0	-	3	100.0 (29.2, 100.0)	15	100.0 (78.2, 100.0)
No	0	-	0	0.0	0	0.0
I don't know	0	-	0	0.0	0	0.0
9e: Chronic non-cancer pain						
No [1]	0	-	1	33.3 (0.8, 90.6)	7	46.7 (21.3, 73.4)
Yes	0	-	2	66.7	8	53.3
I don't know	0	-	0	0.0	0	0.0

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=3		S-4c ≥ 20 min N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.						
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks. [1]	0	-	1	33.3 (0.8, 90.6)	11	73.3 (44.9, 92.2)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	0	-	1	33.3	1	6.7
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	0	-	1	33.3	0	0.0
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	0	-	0	0.0	1	6.7
I don't know	0	-	0	0.0	2	13.3

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY – TELEPHONE:

- **S-4a - <10 min**
- **S-4b – 10 to <20 min**
- **S-4c – ≥ 20 min**

Demonstrated Understanding	S-4a <10 min N=0		S-4b 10 to <20 min N=3		S-4c ≥ 20 min N=15	
	N	%	N	%	N	%
0 correct responses	0	-	0	0.0	0	0.0
1 correct response	0	-	0	0.0	0	0.0
2 correct responses	0	-	1	33.3	0	0.0
3 correct responses	0	-	1	33.3	0	0.0
4 correct responses	0	-	0	0.0	3	20.0
5 correct responses	0	-	1	33.3	8	53.3
6 correct responses	0	-	0	0.0	4	26.7

Demonstrated Understanding	S-4a <10 min N=0		S-4b 10 to <20 min N=3		S-4c ≥ 20 min N=15	
	N	%	N	%	N	%
Average number of correct responses	-		3.3 (1.6, 6.0) [1]		5.1 (4.1, 6.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY – TELEPHONE:

- **S-4a - <10 min**
- **S-4b – 10 to <20 min**
- **S-4c – ≥ 20 min**

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=3		S-4c ≥ 20 min N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.						
True [1]	0	-	3	100.0 (29.2, 100.0)	15	100.0 (78.2, 100.0)
False	0	-	0	0.0	0	0.0
I don't know	0	-	0	0.0	0	0.0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.						
8a: A personal history of psychiatric illness						
Yes [1]	0	-	0	0.0	11	73.3 (44.9, 92.2)
No	0	-	1	33.3	2	13.3
I don't know	0	-	2	66.7	2	13.3
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse						

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=3		S-4c ≥ 20 min N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Yes [1]	0	-	3	100.0 (29.2, 100.0)	14	93.3 (68.1, 99.8)
No	0	-	0	0.0	1	6.7
I don't know	0	-	0	0.0	0	0.0
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.						
True [1]	0	-	3	100.0 (29.2, 100.0)	15	100.0 (78.2, 100.0)
False	0	-	0	0.0	0	0.0
I don't know	0	-	0	0.0	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY – TELEPHONE:

- **S-4a - <10 min**
- **S-4b – 10 to <20 min**
- **S-4c – ≥ 20 min**

Demonstrated Understanding	S-4a <10 min N=0		S-4b 10 to <20 min N=3		S-4c ≥ 20 min N=15	
	N	%	N	%	N	%
0 correct responses	0	-	0	0.0	0	0.0
1 correct response	0	-	0	0.0	0	0.0
2 correct responses	0	-	0	0.0	1	6.7
3 correct responses	0	-	3	100.0	3	20.0
4 correct responses	0	-	0	0.0	11	73.3
Average number of correct responses	-		3.0 (1.4, 4.0) [1]		3.7 (2.9, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY – TELEPHONE:

- **S-4a - <10 min**
- **S-4b – 10 to <20 min**
- **S-4c – ≥ 20 min**

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=3		S-4c ≥ 20 min N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
10b: TIRF medicines are interchangeable with each other regardless of route of administration.						
False [1]	0	-	3	100.0 (29.2, 100.0)	14	93.3 (68.1, 99.8)
True	0	-	0	0.0	0	0.0
I don't know	0	-	0	0.0	1	6.7
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.						
True [1]	0	-	3	100.0 (29.2, 100.0)	14	93.3 (68.1, 99.8)
False	0	-	0	0.0	0	0.0
I don't know	0	-	0	0.0	1	6.7

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=3		S-4c ≥ 20 min N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.						
True [1]	0	-	3	100.0 (29.2, 100.0)	14	93.3 (68.1, 99.8)
False	0	-	0	0.0	1	6.7
I don't know	0	-	0	0.0	0	0.0
Question 14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.						
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose. [1]	0	-	2	66.7 (9.4, 99.2)	8	53.3 (26.6, 78.7)
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	0	-	1	33.3	4	26.7
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	0	-	0	0.0	1	6.7

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=3		S-4c ≥ 20 min N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	0	-	0	0.0	1	6.7
I don't know.	0	-	0	0.0	1	6.7

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 9.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY – TELEPHONE:

- **S-4a - <10 min**
- **S-4b – 10 to <20 min**
- **S-4c – ≥ 20 min**

Demonstrated Understanding	S-4a <10 min N=0		S-4b 10 to <20 min N=3		S-4c ≥ 20 min N=15	
	N	%	N	%	N	%
0 correct responses	0	-	0	0.0	0	0.0
1 correct response	0	-	0	0.0	1	6.7
2 correct responses	0	-	0	0.0	1	6.7
3 correct responses	0	-	1	33.3	5	33.3
4 correct responses	0	-	2	66.7	8	53.3
Average number of correct responses	-		3.7 (1.8, 4.0) [1]		3.3 (2.6, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 6.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Question	S-5a Internet N=282		S-5b Telephone N=18	
	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:				
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer				
True [1]	256	90.8 (86.8, 93.9)	14	77.8 (52.4, 93.6)
False	20	7.1	2	11.1
I don't know	6	2.1	2	11.1
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before				
False [1]	250	88.7 (84.4, 92.1)	11	61.1 (35.7, 82.7)
True	17	6.0	7	38.9
I don't know	15	5.3	0	0.0
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy				
False [1]	249	88.3 (84.0, 91.8)	10	55.6 (30.8, 78.5)
True	21	7.4	7	38.9
I don't know	12	4.3	1	5.6

Question	S-5a Internet N=282		S-5b Telephone N=18	
	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.				
True [1]	243	86.2 (81.6, 90.0)	17	94.4 (72.7, 99.9)
False	31	11.0	1	5.6
I don't know	8	2.8	0	0.0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.				
True [1]	269	95.4 (92.2, 97.5)	18	100.0 (81.5, 100.0)
False	2	0.7	0	0.0
I don't know	11	3.9	0	0.0
7c: TIRF medicines may be used to treat opioid non-tolerant patients.				
False [1]	230	81.6 (76.5, 85.9)	16	88.9 (65.3, 98.6)
True	44	15.6	2	11.1
I don't know	8	2.8	0	0.0
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.				
True [1]	237	84.0 (79.2, 88.1)	15	83.3 (58.6, 96.4)
False	39	13.8	3	16.7
I don't know	6	2.1	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 6.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Demonstrated Understanding	S-5a Internet N=282		S-5b Telephone N=18	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	1	0.4	0	0.0
2 correct responses	4	1.4	0	0.0
3 correct responses	6	2.1	2	11.1
4 correct responses	12	4.3	3	16.7
5 correct responses	37	13.1	2	11.1
6 correct responses	80	28.4	4	22.2
7 correct responses	142	50.4	7	38.9
Average number of correct responses	6.1 (5.9, 7.0) [1]		5.6 (4.7, 7.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 7.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Question	S-5a Internet N=282		S-5b Telephone N=18	
	N	% (95% CI)	N	% (95% CI)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.				
9a: Acute or postoperative pain				
No [1]	246	87.2 (82.8, 90.9)	16	88.9 (65.3, 98.6)
Yes	35	12.4	2	11.1
I don't know	1	0.4	0	0.0
9b: Headache or migraine pain				
No [1]	253	89.7 (85.6, 93.0)	16	88.9 (65.3, 98.6)
Yes	29	10.3	2	11.1
I don't know	0	0.0	0	0.0

Question	S-5a Internet N=282		S-5b Telephone N=18	
	N	% (95% CI)	N	% (95% CI)
9c: Dental pain				
No [1]	276	97.9 (95.4, 99.2)	16	88.9 (65.3, 98.6)
Yes	6	2.1	2	11.1
I don't know	0	0.0	0	0.0
9d: Breakthrough pain from cancer				
Yes [1]	270	95.7 (92.7, 97.8)	18	100.0 (81.5, 100.0)
No	12	4.3	0	0.0
I don't know	0	0.0	0	0.0
9e: Chronic non-cancer pain				
No [1]	178	63.1 (57.2, 68.8)	8	44.4 (21.5, 69.2)
Yes	102	36.2	10	55.6
I don't know	2	0.7	0	0.0

Question	S-5a Internet N=282		S-5b Telephone N=18	
	N	% (95% CI)	N	% (95% CI)
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.				
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks. [1]	187	66.3 (60.5, 71.8)	12	66.7 (41.0, 86.7)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	28	9.9	2	11.1
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	18	6.4	1	5.6
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	21	7.4	1	5.6
I don't know	28	9.9	2	11.1

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Demonstrated Understanding	S-5a Internet N=282		S-5b Telephone N=18	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	3	1.1	0	0.0
2 correct responses	3	1.1	1	5.6
3 correct responses	19	6.7	1	5.6
4 correct responses	45	16.0	3	16.7
5 correct responses	108	38.3	9	50.0
6 correct responses	104	36.9	4	22.2
Average number of correct responses	5.0 (4.8, 6.0) [1]		4.8 (3.9, 6.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Question	S-5a Internet N=282		S-5b Telephone N=18	
	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.				
True [1]	281	99.6 (98.0, 100.0)	18	100.0 (81.5, 100.0)
False	1	0.4	0	0.0
I don't know	0	0.0	0	0.0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.				
8a: A personal history of psychiatric illness				
Yes [1]	241	85.5 (80.8, 89.4)	11	61.1 (35.7, 82.7)
No	20	7.1	3	16.7
I don't know	21	7.4	4	22.2

Question	S-5a Internet N=282		S-5b Telephone N=18	
	N	% (95% CI)	N	% (95% CI)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse				
Yes [1]	282	100.0 (98.7, 100.0)	17	94.4 (72.7, 99.9)
No	0	0.0	1	5.6
I don't know	0	0.0	0	0.0
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.				
True [1]	274	97.2 (94.5, 98.8)	18	100.0 (81.5, 100.0)
False	7	2.5	0	0.0
I don't know	1	0.4	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Demonstrated Understanding	S-5a Internet N=282		S-5b Telephone N=18	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0
2 correct responses	4	1.4	1	5.6
3 correct responses	42	14.9	6	33.3
4 correct responses	236	83.7	11	61.1
Average number of correct responses	3.8 (3.6, 4.0) [1]		3.6 (2.8, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Question	S-5a Internet N=282		S-5b Telephone N=18	
	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
10b: TIRF medicines are interchangeable with each other regardless of route of administration.				
False [1]	262	92.9 (89.3, 95.6)	17	94.4 (72.7, 99.9)
True	15	5.3	0	0.0
I don't know	5	1.8	1	5.6
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.				
True [1]	273	96.8 (94.0, 98.5)	17	94.4 (72.7, 99.9)
False	6	2.1	0	0.0
I don't know	3	1.1	1	5.6
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.				
True [1]	255	90.4 (86.4, 93.6)	17	94.4 (72.7, 99.9)
False	17	6.0	1	5.6
I don't know	10	3.5	0	0.0

Question	S-5a Internet N=282		S-5b Telephone N=18	
	N	% (95% CI)	N	% (95% CI)
Question 14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.				
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose. [1]	213	75.5 (70.1, 80.4)	10	55.6 (30.8, 78.5)
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	21	7.4	5	27.8
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	2	0.7	1	5.6
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	31	11.0	1	5.6
I don't know.	15	5.3	1	5.6

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 9.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Demonstrated Understanding	S-5a Internet N=282		S-5b Telephone N=18	
	N	%	N	%
0 correct responses	2	0.7	0	0.0
1 correct response	6	2.1	1	5.6
2 correct responses	17	6.0	1	5.6
3 correct responses	65	23.0	6	33.3
4 correct responses	192	68.1	10	55.6
Average number of correct responses	3.6 (3.4, 4.0) [1]		3.4 (2.7, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 6.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 6: TIME PRACTICING MEDICINE (QUESTION 33):

- **S-6a - Less than 3 years**
- **S-6b - 3 to 5 years**
- **S-6c - 6 to 15 years**
- **S-6d - More than 15 years**

Question	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:								
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer								
True [1]	25	83.3 (65.3, 94.4)	31	88.6 (73.3, 96.8)	99	90.0 (82.8, 94.9)	113	91.9 (85.6, 96.0)
False	5	16.7	4	11.4	7	6.4	6	4.9
I don't know	0	0.0	0	0.0	4	3.6	4	3.3

Question	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before								
False [1]	28	93.3 (77.9, 99.2)	29	82.9 (66.4, 93.4)	92	83.6 (75.4, 90.0)	110	89.4 (82.6, 94.3)
True	2	6.7	1	2.9	12	10.9	9	7.3
I don't know	0	0.0	5	14.3	6	5.5	4	3.3
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy								
False [1]	23	76.7 (57.7, 90.1)	33	94.3 (80.8, 99.3)	91	82.7 (74.3, 89.3)	110	89.4 (82.6, 94.3)
True	5	16.7	2	5.7	11	10.0	10	8.1
I don't know	2	6.7	0	0.0	8	7.3	3	2.4

Question	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.								
True [1]	27	90.0 (73.5, 97.9)	29	82.9 (66.4, 93.4)	94	85.5 (77.5, 91.5)	108	87.8 (80.7, 93.0)
False	2	6.7	4	11.4	12	10.9	14	11.4
I don't know	1	3.3	2	5.7	4	3.6	1	0.8
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.								
True [1]	29	96.7 (82.8, 99.9)	33	94.3 (80.8, 99.3)	103	93.6 (87.3, 97.4)	120	97.6 (93.0, 99.5)
False	0	0.0	0	0.0	0	0.0	2	1.6
I don't know	1	3.3	2	5.7	7	6.4	1	0.8

Question	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
7c: TIRF medicines may be used to treat opioid non-tolerant patients.								
False [1]	25	83.3 (65.3, 94.4)	31	88.6 (73.3, 96.8)	88	80.0 (71.3, 87.0)	100	81.3 (73.3, 87.8)
True	4	13.3	3	8.6	18	16.4	21	17.1
I don't know	1	3.3	1	2.9	4	3.6	2	1.6
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.								
True [1]	25	83.3 (65.3, 94.4)	28	80.0 (63.1, 91.6)	97	88.2 (80.6, 93.6)	100	81.3 (73.3, 87.8)
False	5	16.7	4	11.4	13	11.8	20	16.3
I don't know	0	0.0	3	8.6	0	0.0	3	2.4

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 6.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 6: TIME PRACTICING MEDICINE (QUESTION 33):

- **S-6a - Less than 3 years**
- **S-6b - 3 to 5 years**
- **S-6c - 6 to 15 years**
- **S-6d - More than 15 years**

Demonstrated Understanding	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	1	0.9	0	0.0
2 correct responses	0	0.0	1	2.9	1	0.9	2	1.6
3 correct responses	1	3.3	1	2.9	3	2.7	3	2.4
4 correct responses	1	3.3	0	0.0	9	8.2	5	4.1
5 correct responses	5	16.7	4	11.4	14	12.7	16	13.0
6 correct responses	11	36.7	14	40.0	28	25.5	31	25.2
7 correct responses	12	40.0	15	42.9	54	49.1	66	53.7
Average number of correct responses	6.1 (5.3, 7.0) [1]		6.1 (5.4, 7.0) [1]		6.0 (5.7, 7.0) [1]		6.2 (5.8, 7.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 7.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 6: TIME PRACTICING MEDICINE (QUESTION 33):

- **S-6a - Less than 3 years**
- **S-6b - 3 to 5 years**
- **S-6c - 6 to 15 years**
- **S-6d - More than 15 years**

Question	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.								
9a: Acute or postoperative pain								
No [1]	29	96.7 (82.8, 99.9)	31	88.6 (73.3, 96.8)	93	84.5 (76.4, 90.7)	107	87.0 (79.7, 92.4)
Yes	1	3.3	4	11.4	16	14.5	16	13.0
I don't know	0	0.0	0	0.0	1	0.9	0	0.0

Question	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9b: Headache or migraine pain								
No [1]	27	90.0 (73.5, 97.9)	31	88.6 (73.3, 96.8)	101	91.8 (85.0, 96.2)	108	87.8 (80.7, 93.0)
Yes	3	10.0	4	11.4	9	8.2	15	12.2
I don't know	0	0.0	0	0.0	0	0.0	0	0.0
9c: Dental pain								
No [1]	30	100.0 (88.4, 100.0)	34	97.1 (85.1, 99.9)	108	98.2 (93.6, 99.8)	118	95.9 (90.8, 98.7)
Yes	0	0.0	1	2.9	2	1.8	5	4.1
I don't know	0	0.0	0	0.0	0	0.0	0	0.0
9d: Breakthrough pain from cancer								
Yes [1]	29	96.7 (82.8, 99.9)	32	91.4 (76.9, 98.2)	108	98.2 (93.6, 99.8)	117	95.1 (89.7, 98.2)
No	1	3.3	3	8.6	2	1.8	6	4.9
I don't know	0	0.0	0	0.0	0	0.0	0	0.0

Question	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9e: Chronic non-cancer pain								
No [1]	22	73.3 (54.1, 87.7)	20	57.1 (39.4, 73.7)	79	71.8 (62.4, 80.0)	63	51.2 (42.0, 60.3)
Yes	8	26.7	14	40.0	30	27.3	60	48.8
I don't know	0	0.0	1	2.9	1	0.9	0	0.0
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.								
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks. [1]	19	63.3 (43.9, 80.1)	25	71.4 (53.7, 85.4)	66	60.0 (50.2, 69.2)	87	70.7 (61.9, 78.6)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	4	13.3	4	11.4	15	13.6	7	5.7

Question	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	2	6.7	2	5.7	7	6.4	8	6.5
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	4	13.3	1	2.9	12	10.9	5	4.1
I don't know	1	3.3	3	8.6	10	9.1	16	13.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 6: TIME PRACTICING MEDICINE (QUESTION 33):

- **S-6a - Less than 3 years**
- **S-6b - 3 to 5 years**
- **S-6c - 6 to 15 years**
- **S-6d - More than 15 years**

Demonstrated Understanding	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	1	2.9	0	0.0	2	1.6
2 correct responses	0	0.0	0	0.0	3	2.7	1	0.8
3 correct responses	1	3.3	3	8.6	5	4.5	11	8.9
4 correct responses	5	16.7	5	14.3	20	18.2	18	14.6
5 correct responses	11	36.7	13	37.1	38	34.5	55	44.7

Demonstrated Understanding	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	%	N	%	N	%	N	%
6 correct responses	13	43.3	13	37.1	44	40.0	36	29.3
Average number of correct responses	5.2 (4.5, 6.0) [1]		4.9 (4.3, 6.0) [1]		5.0 (4.7, 6.0) [1]		4.9 (4.6, 6.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 6: TIME PRACTICING MEDICINE (QUESTION 33):

- **S-6a - Less than 3 years**
- **S-6b - 3 to 5 years**
- **S-6c - 6 to 15 years**
- **S-6d - More than 15 years**

Question	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.								
True [1]	30	100.0 (88.4, 100.0)	35	100.0 (90.0, 100.0)	110	100.0 (96.7, 100.0)	122	99.2 (95.6, 100.0)
False	0	0.0	0	0.0	0	0.0	1	0.8
I don't know	0	0.0	0	0.0	0	0.0	0	0.0

Question	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.								
8a: A personal history of psychiatric illness								
Yes [1]	27	90.0 (73.5, 97.9)	28	80.0 (63.1, 91.6)	91	82.7 (74.3, 89.3)	104	84.6 (76.9, 90.4)
No	2	6.7	3	8.6	9	8.2	9	7.3
I don't know	1	3.3	4	11.4	10	9.1	10	8.1
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse								
Yes [1]	30	100.0 (88.4, 100.0)	35	100.0 (90.0, 100.0)	109	99.1 (95.0, 100.0)	123	100.0 (97.0, 100.0)
No	0	0.0	0	0.0	1	0.9	0	0.0
I don't know	0	0.0	0	0.0	0	0.0	0	0.0

Question	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.								
True [1]	29	96.7 (82.8, 99.9)	35	100.0 (90.0, 100.0)	105	95.5 (89.7, 98.5)	121	98.4 (94.2, 99.8)
False	0	0.0	0	0.0	5	4.5	2	1.6
I don't know	1	3.3	0	0.0	0	0.0	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 6: TIME PRACTICING MEDICINE (QUESTION 33):

- **S-6a - Less than 3 years**
- **S-6b - 3 to 5 years**
- **S-6c - 6 to 15 years**
- **S-6d - More than 15 years**

Demonstrated Understanding	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	0	0.0	0	0.0
2 correct responses	0	0.0	0	0.0	4	3.6	1	0.8
3 correct responses	4	13.3	7	20.0	17	15.5	20	16.3
4 correct responses	26	86.7	28	80.0	89	80.9	102	82.9
Average number of correct responses	3.9 (3.3, 4.0) [1]		3.8 (3.3, 4.0) [1]		3.8 (3.5, 4.0) [1]		3.8 (3.5, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 6: TIME PRACTICING MEDICINE (QUESTION 33):

- **S-6a - Less than 3 years**
- **S-6b - 3 to 5 years**
- **S-6c - 6 to 15 years**
- **S-6d - More than 15 years**

Question	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
10b: TIRF medicines are interchangeable with each other regardless of route of administration.								
False [1]	29	96.7 (82.8, 99.9)	33	94.3 (80.8, 99.3)	99	90.0 (82.8, 94.9)	116	94.3 (88.6, 97.7)
True	1	3.3	2	5.7	7	6.4	5	4.1
I don't know	0	0.0	0	0.0	4	3.6	2	1.6

Question	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.								
True [1]	29	96.7 (82.8, 99.9)	33	94.3 (80.8, 99.3)	107	97.3 (92.2, 99.4)	119	96.7 (91.9, 99.1)
False	0	0.0	1	2.9	3	2.7	2	1.6
I don't know	1	3.3	1	2.9	0	0.0	2	1.6
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.								
True [1]	26	86.7 (69.3, 96.2)	30	85.7 (69.7, 95.2)	101	91.8 (85.0, 96.2)	113	91.9 (85.6, 96.0)
False	2	6.7	2	5.7	6	5.5	8	6.5
I don't know	2	6.7	3	8.6	3	2.7	2	1.6

Question	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.								
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose. [1]	23	76.7 (57.7, 90.1)	29	82.9 (66.4, 93.4)	80	72.7 (63.4, 80.8)	89	72.4 (63.6, 80.0)
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	1	3.3	1	2.9	8	7.3	16	13.0
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	0	0.0	0	0.0	1	0.9	2	1.6

Question	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	3	10.0	3	8.6	15	13.6	11	8.9
I don't know.	3	10.0	2	5.7	6	5.5	5	4.1

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 9.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 6: TIME PRACTICING MEDICINE (QUESTION 33):

- **S-6a - Less than 3 years**
- **S-6b - 3 to 5 years**
- **S-6c - 6 to 15 years**
- **S-6d - More than 15 years**

Demonstrated Understanding	S-6a Less than 3 years N=30		S-6b 3 to 5 years N=35		S-6c 6 to 15 years N=110		S-6d More than 15 years N=123	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	1	0.9	1	0.8
1 correct response	0	0.0	2	5.7	1	0.9	4	3.3
2 correct responses	4	13.3	2	5.7	6	5.5	6	4.9
3 correct responses	5	16.7	5	14.3	34	30.9	27	22.0
4 correct responses	21	70.0	26	74.3	68	61.8	85	69.1
Average number of correct responses	3.6 (3.0, 4.0) [1]		3.6 (3.0, 4.0) [1]		3.5 (3.2, 4.0) [1]		3.6 (3.3, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 6.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 7: NUMBER OF TIMES PER MONTHS PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 29):

- **S-7a - None**
- **S-7b - 1 - 2 times a month**
- **S-7c - 3 - 5 times a month**
- **S-7d - More than 5 times a month**

Question	S-7a None N=64		S-7b 1– 2 times per month N=154		S-7c 3– 5 times per month N=45		S-7d More than 5 times per month N=26	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:								
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer								
True [1]	59	92.2 (82.7, 97.4)	140	90.9 (85.2, 94.9)	40	88.9 (75.9, 96.3)	21	80.8 (60.6, 93.4)
False	2	3.1	13	8.4	3	6.7	4	15.4
I don't know	3	4.7	1	0.6	2	4.4	1	3.8

Question	S-7a None N=64		S-7b 1– 2 times per month N=154		S-7c 3– 5 times per month N=45		S-7d More than 5 times per month N=26	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before								
False [1]	53	82.8 (71.3, 91.1)	136	88.3 (82.2, 92.9)	39	86.7 (73.2, 94.9)	23	88.5 (69.8, 97.6)
True	5	7.8	13	8.4	3	6.7	3	11.5
I don't know	6	9.4	5	3.2	3	6.7	0	0.0
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy								
False [1]	54	84.4 (73.1, 92.2)	134	87.0 (80.7, 91.9)	38	84.4 (70.5, 93.5)	23	88.5 (69.8, 97.6)
True	5	7.8	14	9.1	6	13.3	3	11.5
I don't know	5	7.8	6	3.9	1	2.2	0	0.0
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.								
True [1]	53	82.8 (71.3, 91.1)	137	89.0 (82.9, 93.4)	37	82.2 (67.9, 92.0)	23	88.5 (69.8, 97.6)
False	8	12.5	14	9.1	7	15.6	3	11.5
I don't know	3	4.7	3	1.9	1	2.2	0	0.0

Question	S-7a None N=64		S-7b 1– 2 times per month N=154		S-7c 3– 5 times per month N=45		S-7d More than 5 times per month N=26	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.								
True [1]	61	95.3 (86.9, 99.0)	148	96.1 (91.7, 98.6)	43	95.6 (84.9, 99.5)	26	100.0 (86.8, 100.0)
False	0	0.0	2	1.3	0	0.0	0	0.0
I don't know	3	4.7	4	2.6	2	4.4	0	0.0
7c: TIRF medicines may be used to treat opioid non-tolerant patients.								
False [1]	51	79.7 (67.8, 88.7)	125	81.2 (74.1, 87.0)	37	82.2 (67.9, 92.0)	23	88.5 (69.8, 97.6)
True	10	15.6	26	16.9	8	17.8	2	7.7
I don't know	3	4.7	3	1.9	0	0.0	1	3.8
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.								
True [1]	55	85.9 (75.0, 93.4)	129	83.8 (77.0, 89.2)	39	86.7 (73.2, 94.9)	20	76.9 (56.4, 91.0)
False	6	9.4	22	14.3	6	13.3	6	23.1
I don't know	3	4.7	3	1.9	0	0.0	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 6.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 7: NUMBER OF TIMES PER MONTHS PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 29):

- **S-7a - None**
- **S-7b - 1 - 2 times a month**
- **S-7c - 3 - 5 times a month**
- **S-7d - More than 5 times a month**

Demonstrated Understanding	S-7a None N=64		S-7b 1-2 times a month N=154		S-7c 3 - 5 times a month N=45		S-7d More than 5 times a month N=26	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	0	0.0	0	0.0
2 correct responses	2	3.1	1	0.6	1	2.2	0	0.0
3 correct responses	2	3.1	4	2.6	1	2.2	1	3.8
4 correct responses	5	7.8	5	3.2	3	6.7	2	7.7
5 correct responses	7	10.9	23	14.9	7	15.6	1	3.8
6 correct responses	15	23.4	47	30.5	10	22.2	11	42.3
7 correct responses	33	51.6	74	48.1	23	51.1	11	42.3

Demonstrated Understanding	S-7a None N=64		S-7b 1-2 times a month N=154		S-7c 3 - 5 times a month N=45		S-7d More than 5 times a month N=26	
	N	%	N	%	N	%	N	%
Average number of correct responses	6.0 (5.5, 7.0) [1]		6.2 (5.8, 7.0) [1]		6.1 (5.5, 7.0) [1]		6.1 (5.3, 7.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 7.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 7: NUMBER OF TIMES PER MONTHS PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 29):

- **S-7a - None**
- **S-7b - 1 - 2 times a month**
- **S-7c - 3 - 5 times a month**
- **S-7d - More than 5 times a month**

Question	S-7a None N=64		S-7b 1-2 times a month N=154		S-7c 3 - 5 times a month N=45		S-7d More than 5 times a month N=26	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.								
9a: Acute or postoperative pain								
No [1]	56	87.5 (76.8, 94.4)	132	85.7 (79.2, 90.8)	42	93.3 (81.7, 98.6)	22	84.6 (65.1, 95.6)
Yes	8	12.5	21	13.6	3	6.7	4	15.4
I don't know	0	0.0	1	0.6	0	0.0	0	0.0
9b: Headache or migraine pain								
No [1]	63	98.4 (91.6, 100.0)	134	87.0 (80.7, 91.9)	41	91.1 (78.8, 97.5)	23	88.5 (69.8, 97.6)
Yes	1	1.6	20	13.0	4	8.9	3	11.5
I don't know	0	0.0	0	0.0	0	0.0	0	0.0

Question	S-7a None N=64		S-7b 1-2 times a month N=154		S-7c 3 - 5 times a month N=45		S-7d More than 5 times a month N=26	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9c: Dental pain								
No [1]	64	100.0 (94.4, 100.0)	149	96.8 (92.6, 98.9)	44	97.8 (88.2, 99.9)	25	96.2 (80.4, 99.9)
Yes	0	0.0	5	3.2	1	2.2	1	3.8
I don't know	0	0.0	0	0.0	0	0.0	0	0.0
9d: Breakthrough pain from cancer								
Yes [1]	62	96.9 (89.2, 99.6)	149	96.8 (92.6, 98.9)	44	97.8 (88.2, 99.9)	24	92.3 (74.9, 99.1)
No	2	3.1	5	3.2	1	2.2	2	7.7
I don't know	0	0.0	0	0.0	0	0.0	0	0.0
9e: Chronic non-cancer pain								
No [1]	52	81.3 (69.5, 89.9)	95	61.7 (53.5, 69.4)	22	48.9 (33.7, 64.2)	10	38.5 (20.2, 59.4)
Yes	12	18.8	58	37.7	23	51.1	16	61.5
I don't know	0	0.0	1	0.6	0	0.0	0	0.0

Question	S-7a None N=64		S-7b 1-2 times a month N=154		S-7c 3 - 5 times a month N=45		S-7d More than 5 times a month N=26	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.								
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks. [1]	29	45.3 (32.8, 58.3)	105	68.2 (60.2, 75.4)	37	82.2 (67.9, 92.0)	21	80.8 (60.6, 93.4)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	9	14.1	16	10.4	2	4.4	2	7.7

Question	S-7a None N=64		S-7b 1-2 times a month N=154		S-7c 3 - 5 times a month N=45		S-7d More than 5 times a month N=26	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	9	14.1	6	3.9	3	6.7	1	3.8
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	7	10.9	13	8.4	1	2.2	0	0.0
I don't know	10	15.6	14	9.1	2	4.4	2	7.7

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 7: NUMBER OF TIMES PER MONTHS PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 29):

- **S-7a - None**
- **S-7b - 1 - 2 times a month**
- **S-7c - 3 - 5 times a month**
- **S-7d - More than 5 times a month**

Demonstrated Understanding	S-7a None N=64		S-7b 1-2 times a month N=154		S-7c 3 - 5 times a month N=45		S-7d More than 5 times a month N=26	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	2	1.3	0	0.0	0	0.0
2 correct responses	0	0.0	3	1.9	0	0.0	0	0.0
3 correct responses	1	1.6	15	9.7	1	2.2	3	11.5
4 correct responses	14	21.9	20	13.0	9	20.0	4	15.4

Demonstrated Understanding	S-7a None N=64		S-7b 1-2 times a month N=154		S-7c 3 - 5 times a month N=45		S-7d More than 5 times a month N=26	
	N	%	N	%	N	%	N	%
5 correct responses	27	42.2	53	34.4	19	42.2	14	53.8
6 correct responses	22	34.4	61	39.6	16	35.6	5	19.2
Average number of correct responses	5.1 (4.6, 6.0) [1]		5.0 (4.7, 6.0) [1]		5.1 (4.6, 6.0) [1]		4.8 (4.1, 6.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 7: NUMBER OF TIMES PER MONTHS PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 29):

- **S-7a - None**
- **S-7b - 1 - 2 times a month**
- **S-7c - 3 - 5 times a month**
- **S-7d - More than 5 times a month**

Question	S-7a None N=64		S-7b 1-2 times a month N=154		S-7c 3 - 5 times a month N=45		S-7d More than 5 times a month N=26	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.								
True [1]	63	98.4 (91.6, 100.0)	154	100.0 (97.6, 100.0)	45	100.0 (92.1, 100.0)	26	100.0 (86.8, 100.0)
False	1	1.6	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0	0	0.0

Question	S-7a None N=64		S-7b 1-2 times a month N=154		S-7c 3 - 5 times a month N=45		S-7d More than 5 times a month N=26	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.								
8a: A personal history of psychiatric illness								
Yes [1]	50	78.1 (66.0, 87.5)	135	87.7 (81.4, 92.4)	37	82.2 (67.9, 92.0)	19	73.1 (52.2, 88.4)
No	6	9.4	10	6.5	4	8.9	3	11.5
I don't know	8	12.5	9	5.8	4	8.9	4	15.4
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse								
Yes [1]	64	100.0 (94.4, 100.0)	154	100.0 (97.6, 100.0)	45	100.0 (92.1, 100.0)	25	96.2 (80.4, 99.9)
No	0	0.0	0	0.0	0	0.0	1	3.8
I don't know	0	0.0	0	0.0	0	0.0	0	0.0

Question	S-7a None N=64		S-7b 1-2 times a month N=154		S-7c 3 - 5 times a month N=45		S-7d More than 5 times a month N=26	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.								
True [1]	60	93.8 (84.8, 98.3)	151	98.1 (94.4, 99.6)	44	97.8 (88.2, 99.9)	26	100.0 (86.8, 100.0)
False	3	4.7	3	1.9	1	2.2	0	0.0
I don't know	1	1.6	0	0.0	0	0.0	0	0.0

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II-CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 7: NUMBER OF TIMES PER MONTHS PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 29):

- **S-7a - None**
- **S-7b - 1 - 2 times a month**
- **S-7c - 3 - 5 times a month**
- **S-7d - More than 5 times a month**

Demonstrated Understanding	S-7a None N=64		S-7b 1-2 times a month N=154		S-7c 3 - 5 times a month N=45		S-7d More than 5 times a month N=26	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	0	0.0	0	0.0
2 correct responses	3	4.7	1	0.6	0	0.0	1	3.8
3 correct responses	13	20.3	20	13.0	9	20.0	6	23.1
4 correct responses	48	75.0	133	86.4	36	80.0	19	73.1
Average number of correct responses	3.7 (3.3, 4.0) [1]		3.9 (3.6, 4.0) [1]		3.8 (3.3, 4.0) [1]		3.7 (3.1, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

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Client: TRIG Project: TIRF Wave 3

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TABLE 9.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 7: NUMBER OF TIMES PER MONTHS PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 29):

- **S-7a - None**
- **S-7b - 1 - 2 times a month**
- **S-7c - 3 - 5 times a month**
- **S-7d - More than 5 times a month**

Question	S-7a None N=64		S-7b 1-2 times a month N=154		S-7c 3 - 5 times a month N=45		S-7d More than 5 times a month N=26	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
10b: TIRF medicines are interchangeable with each other regardless of route of administration.								
False [1]	59	92.2 (82.7, 97.4)	142	92.2 (86.8, 95.9)	42	93.3 (81.7, 98.6)	25	96.2 (80.4, 99.9)
True	3	4.7	10	6.5	1	2.2	1	3.8
I don't know	2	3.1	2	1.3	2	4.4	0	0.0

Question	S-7a None N=64		S-7b 1-2 times a month N=154		S-7c 3 - 5 times a month N=45		S-7d More than 5 times a month N=26	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.								
True [1]	59	92.2 (82.7, 97.4)	150	97.4 (93.5, 99.3)	44	97.8 (88.2, 99.9)	26	100.0 (86.8, 100.0)
False	4	6.3	2	1.3	0	0.0	0	0.0
I don't know	1	1.6	2	1.3	1	2.2	0	0.0
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.								
True [1]	56	87.5 (76.8, 94.4)	139	90.3 (84.4, 94.4)	42	93.3 (81.7, 98.6)	26	100.0 (86.8, 100.0)
False	6	9.4	10	6.5	1	2.2	0	0.0
I don't know	2	3.1	5	3.2	2	4.4	0	0.0

Question	S-7a None N=64		S-7b 1-2 times a month N=154		S-7c 3 - 5 times a month N=45		S-7d More than 5 times a month N=26	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.								
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose. [1]	47	73.4 (60.9, 83.7)	117	76.0 (68.4, 82.5)	32	71.1 (55.7, 83.6)	18	69.2 (48.2, 85.7)
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	6	9.4	11	7.1	5	11.1	4	15.4
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	1	1.6	1	0.6	0	0.0	1	3.8

Question	S-7a None N=64		S-7b 1-2 times a month N=154		S-7c 3 - 5 times a month N=45		S-7d More than 5 times a month N=26	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	6	9.4	17	11.0	6	13.3	2	7.7
I don't know.	4	6.3	8	5.2	2	4.4	1	3.8

[1] Correct Response

Note: All confidence intervals are exact binomial 95% confidence intervals.

TABLE 9.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 7: NUMBER OF TIMES PER MONTHS PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 29):

- **S-7a - None**
- **S-7b - 1 - 2 times a month**
- **S-7c - 3 - 5 times a month**
- **S-7d - More than 5 times a month**

Demonstrated Understanding	S-7a None N=64		S-7b 1-2 times a month N=154		S-7c 3 - 5 times a month N=45		S-7d More than 5 times a month N=26	
	N	%	N	%	N	%	N	%
0 correct responses	1	1.6	1	0.6	0	0.0	0	0.0
1 correct response	4	6.3	2	1.3	1	2.2	0	0.0
2 correct responses	1	1.6	14	9.1	2	4.4	1	3.8
3 correct responses	17	26.6	30	19.5	13	28.9	7	26.9
4 correct responses	41	64.1	107	69.5	29	64.4	18	69.2
Average number of correct responses	3.5 (3.1, 4.0) [1]		3.6 (3.3, 4.0) [1]		3.6 (3.1, 4.0) [1]		3.7 (3.0, 4.0) [1]	

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

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Client: TRIG Project: TIRF Wave 3

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Listing 1 **VERBATIM RESPONSES TO QUESTION 24 (Questions about the information in the full prescribing information or medication guide)**

Verbatim Response
answered last question incorrectly; should have been no
Any guides regarding conversion to alternative TIRF agents is helpful as that is felt to be the most risky time with this med. use.
are there online guides to prescribing
Can patients stop taking their around the clock opioid medications and still continue TIRF products?
Can you continue TRIF meds after stopping long actin meds?
Despite not being 'approved for migraine and acute pain,' I have patients whom I inherited on these medications (for migraine). They work well and I have continued them. As for acute pain, Oral fentanyl has been given in a hospital setting in the recovery room. Why is this not approved?
DOES Erythromycin interfere?
error none
Generally question about cross titration between medications and how to do it more accurately.
How to monitor intake through qualitative UDS if patient taking rarley ?
I asked my rep
I do not prescribe these medications on a regular basis and I do not intend to prescribe them regularly.
i typed yes, on accident
I would like a copy emailed or mailed to have readily available to review.
Is there any upcoming information on conversion ratios of different fentanyl products?
It was a while ago and I do not recall. I do rememeber that my question at that time was answered in regards to the subscribing of the medication.
mainly concerning dosing, titration, and conversions
need close monitoring of these patients any new studies
no questions
No questions.
none
none currently
None now
none right now

Verbatim Response
none.
Not exactly clear about medication interaction with the 3A4 pathway
One type better indicated for certain conditions compared to the others?
Proper starting dose, dose escalation questions
question about whether fentora could be placed sublingual (answer no) since patient had bad dental abscesses that made mucosal placement difficult
The genomic contribution to the problems to Fentanyl and its detoxification profiles as well as its pharmacokinetics is rarely discussed in the past when was that information known?
They were answered by the pharmacology representative visiting office.
they were answered by the rep and pointed out in the medication guide
use of TIRF medicine in noncancerous chronic pain patients?
Who decided which guidelines would be used?
Why do I have to fill out a form each time.

Listing 2 **VERBATIM RESPONSES TO QUESTION 35 (OTHER MEDICAL SPECIALTY)**

Verbatim Response
PMR
office orthopedics
Hospice and Palliative Medicine
Neurology
FIBROMYALGIA
Anesthesia
palliative care
hospice
Hematology
Anesthesiology
Family Practice, Addiction
Palliative Medicine
nephrology
Family practice- pain management
gynecologic oncology
physical medicine
physical medicine and rehab.
rehab/physiatry/pain
oncology and palliative care
Transplant Surgery
Hospital Medicine
PM&R
Palliative /Hospice
Palliative Medicine
Neurosurgery
oncologic emergencies
Pediatric Hematology/Oncology

Verbatim Response
Internal Medicine/Hospice
Physiatry
pain and addiction medicine with osteopathic maniplative medicine
Pediatric Palliative Care
Geriatrics
palliative care and hospice
Physical Medicine and Rehab
geriatrics
Hospice / Palliative Care
hospice and palliative care
HPM

Listing 3 **VERBATIM RESPONSES TO REPORTED ADVERSE EVENTS, PRODUCT COMPLAINTS OR REQUESTS FOR MEDICAL INFORMATION**

Verbatim Response
I don't prescribe Actiq. Actiq causes cavities. I had one patient need dental work.
Any guides regarding conversion to alternative TIRF agents is helpful as that is felt to be the most risky time with this med. use.
are there online guides to prescribing
Can patients stop taking their around the clock opioid medications and still continue TIRF products?
Can you continue TRIF meds after stopping long actin meds?
Despite not being 'approved for migraine and acute pain,' I have patients whom I inherited on these medications (for migraine). They work well and I have continued them. As for acute pain, Oral fentanyl has been given in a hospital setting in the recovery room. Why is this not approved?
DOES Erythromycin interfere?
Generally question about cross titration between medications and how to do it more accurately.
How to monitor intake through qualitative UDS if patient taking rarley ?
I would like a copy emailed or mailed to have readily available to review.
Is there any upcoming information on conversion ratios of different fentanyl products?
mainly concerning dosing, titration, and conversions
Not exactly clear about medication interaction with the 3A4 pathway
One type better indicated for certain conditions compared to the others?
Proper starting dose, dose escalation questions
question about whether fentora could be placed sublingual (answer no) since patient had bad dental abscesses that made mucosal placement difficult
The genomic contribution to the problems to Fentanyl and its detoxification profiles as well as its pharmacokinetics is rarely discussed in the past when was that information known?
use of TIRF medicine in noncancerous chronic pain patients?
Who decided which guidelines would be used?
Why do I have to fill out a form each time.

Appendix C Prescriber Survey Protocol Track Change Document: Comparison of 24-month Survey to 36-month Survey

PROTOCOL TITLE:	**Quantitative Testing of Prescriber Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)**
	Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)
	Depomed, Inc.
	Galena Biopharma, Inc.
	Insys Therapeutics
	Mallinckrodt Pharmaceuticals
	Meda Pharmaceuticals
	Mylan, Inc.
	Par Pharmaceutical, Inc.
VERSION:	**7.0**
DATE:	**25JUL2014**
APPROVED:	**Final**

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TABLE OF CONTENTS **PAGE**

	TABLE OF CONTENTS	2
1.	LIST OF ABBREVIATIONS	3
2.	BACKGROUND	4
3.	OBJECTIVES OF THE EVALUATION SURVEY	5
4.	METHODS	5
4.1	Survey Design	5
4.1.1	Qualitative Research on the Survey	6
4.1.2	Questions on REMS Goals	6
4.1.3	Additional Questions	9
4.2	Participant Recruitment	9
4.2.1	Measures to Minimize Bias in the Sample	10
5.	STUDY POPULATION	10
5.1.1	Sample Size	10
5.1.2	Inclusion Criteria	11
5.1.3	Exclusion Criteria	11
6.	SURVEY PROCESS	11
6.1	Screening and Survey Administration	11
6.1.1	Telephone	12
6.1.2	Internet	12
6.2	Measures to Minimize Bias in the Survey Process	12
7.	ANALYSIS	12
7.1.1	Analysis Population	13
7.1.2	Description of Primary Analyses	13
7.1.3	Description of Secondary Analyses	13
8.	SAFETY EVENT REPORTING	14
9.	PRIVACY PROTECTION AND CONFIDENTIALITY	14

LIST OF APPENDICES

Appendix A	Prescriber Questionnaire	15
Appendix B	SAMPLE Prescriber Invitation Letter	37

1. LIST OF ABBREVIATIONS

CATI	Computer-Assisted Telephone Interviewing
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ISI	Important Safety Information
KAB	Knowledge, Attitudes and Behavior
PI	Prescribing Information
REMS	Risk Evaluation and Mitigation Strategy
SE PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access Program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

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2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by the following:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

2. Preventing inappropriate conversion between TIRF medicines.

3. Preventing accidental exposure to children and others for whom it was not prescribed.

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess prescribers' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS educational materials, enrollment form, and Prescribing Information (PI) of each product. This protocol will describe the administration of the surveys that will be conducted among prescribers who are enrolled in the TIRF REMS Access Program. Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

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The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

3. OBJECTIVES OF THE EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of prescribers around the following key information and risk messages communicated through the REMS:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.
2. TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 or older for Actiq® and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
3. TIRF medicines contain fentanyl, an opioid agonist and a Schedule II-controlled substance, with abuse liability similar to other opioid analgesics.
4. TIRF medicines are not interchangeable with each other, regardless of route of administration.
5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey will also collect data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC) and will be administered by UBC.

4.1 Survey Design

This survey will be conducted among a sample of prescribers who are enrolled in the TIRF REMS Access Program. Respondents who participate in the previous wave of the TIRF survey will not be eligible to participate in subsequent survey waves.

The survey will be administered using the following modalities:

- Self-administered, online through a secure website

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- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

The survey included in Appendix A is written to reflect wording for both methods of survey administration: Internet-based and telephone.

All respondents who complete the survey and who provide their contact information will be mailed a $125 honorarium for their time.

4.1.1 Qualitative Research on the Survey

The FDA provided feedback to the TRIG on the Knowledge, Attitudes and Behaviors (KAB) survey results for prescribers included in the 12-month REMS Assessment results. The FDA requested that the TRIG investigate the causes for low correct response rates to specific questions in the survey by conducting research to determine the reasons for the poor performance on these questions, and to assess proposed revised wording to select questions. Qualitative research was performed in 2013 prior to Wave 2 of the survey. Findings were incorporated into the survey and results from the revised survey were included in the 24-month REMS Assessment Report.

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4.1.2 Questions on REMS Goals

The KAB questionnaire is made up of multiple-choice, close-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and one open-ended question. These will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3.

Deleted: Qualitative research was performed with 7 prescribers who were recruited from the list of prescribers who completed surveys for the 12-month TIRF REMS Assessment and met the definition of "low performer," i e , provided an incorrect response on 3 to 7 of the 10 targeted responses/questions from the 12-month TIRF REMS Assessment ¶
Among the prescribers interviewed, the need to provide a "frame-of-reference" for responding was frequent feedback In addition, some of the findings suggest potential knowledge gap with respect to:¶
<#>Definition of opioid tolerance;¶
<#>How to convert patients from one TIRF medicine to another TIRF medicine; and ¶
<#>Content pertaining to CYP3A4 inhibitors ¶
The findings from this research have been incorporated into the survey in Appendix A The qualitative research report can be found in Appendix C ¶

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Questions will be presented in several formats:

- Statements or questions asking the respondent to indicate whether a statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use "yes" or "no" as potential response options);
- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and
- One question allowing for the respondent to list questions about the products or comments.

Questionnaires will be analyzed to determine prescriber understanding of each key risk message.

For statements or questions that use "true" or "yes" vs. "false" or "no" response options, the desired response for key risk messages is generally "true" or "yes" indicating knowledge of,

or behavior in accordance with, the objectives of the REMS. However, some questions are formatted to have the respondent disagree with the statement as written by providing response options of "false" or "no" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired response**
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a	Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	**TRUE**
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before	**FALSE**
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	**FALSE**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**TRUE**
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	**TRUE**
7c	TIRF medicines may be used to treat opioid non-tolerant patients.	**FALSE**
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	**TRUE**

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.		
Question No.	**Question**	**Desired response**
9	In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a	Acute or postoperative pain	**NO**

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9b	Headache or migraine pain	**NO**
9c	Dental pain	**NO**
9d	Breakthrough pain from cancer	**YES**
9e	Chronic non-cancer pain	**NO**
13	The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.	**13b.** Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.

Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II-controlled substance, with abuse liability similar to other opioid analgesics.

Question No.	Question	Desired response
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**TRUE**
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a	A personal history of psychiatric illness	**YES**
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**YES**
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10a	TIRF medicines can be abused in a manner similar to other opioid agonists.	**TRUE**

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question No.	Question	Desired response
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10b	TIRF medicines are interchangeable with each other regardless of route of administration.	**FALSE**
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in	**TRUE**

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	the pharmacokinetics of fentanyl absorption.	
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**TRUE**
14	A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.	**14b.** The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.

4.1.3 Additional Questions

The survey includes questions about the requirements of the TIRF REMS Access Program and receipt and understanding of the TIRF educational materials and the Patient-Prescriber Agreement Form. The following question about behaviors will be asked after the key risk message questions:

Question 12: How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know
Ask patients (or their caregivers) about the presence of children in the home
Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
Give patients (or their caregivers) the Medication Guide for their TIRF medicine

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Demographic information will be collected at the end of the survey.

4.2 Participant Recruitment

A random sample of prescribers who are enrolled in the TIRF REMS Access Program will be invited to participate via an invitation letter. The text of the sample written invitation to prescribers can be found in Appendix B. If the required number of completed surveys is not achieved within the expected timeframe of approximately one to two weeks after the first mailing, reminder letters will be sent to non-responders from the original sample with subsequent fax, e-mail, or United States (US) Mail follow-up to maximize participation. The distribution within the mailing to the second sample will be adjusted in accordance with the allocation in the original sample. If these efforts do not result in the required number of

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surveys within two to three weeks, then a new sample of prescribers will be randomly selected.

All respondents who complete the survey and who provide their contact information will be mailed a $125 honorarium to thank them for their participation. Prescribers who practice in Vermont, Massachusetts, or Minnesota and complete the survey will not receive compensation. Participants will be informed that prescribers from these states are eligible to participate, but they will not receive compensation for their participation. The mailing will also include a Thank You Letter, a copy of the Important Safety Information (ISI), and a copy of the correct answers to key risk message questions.

4.2.1 Measures to Minimize Bias in the Sample

The sample of prescribers who are invited to participate will be a random sample of all enrolled prescribers. The sample of participating prescribers will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of prescribers for participation.

Prescribers will be offered online or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the online survey or when calling the Survey Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

5. STUDY POPULATION

5.1.1 Sample Size

A sample of 300 healthcare providers who are enrolled in the TIRF REMS Access Program is proposed for each survey wave. The size of the sample was determined based on both practical and statistical considerations. There is no target comprehension rate specified *a priori*. A sample of 300 completed surveys will allow estimation of the comprehension rate for each risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval

5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.2 Inclusion Criteria

All prescribers who are enrolled in the TIRF REMS Access Program are eligible to participate in this survey, with the exceptions noted below.

5.1.3 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Prescribers who have previously participated in the TIRF REMS KAB survey
- Prescribers or their immediate family members who have ever worked for ever worked for Anesta LLC; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd); Depomed Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc.; Par Pharmaceutical, Inc.; Teva Pharmaceuticals, Ltd.; UBC; McKesson Specialty Care Solutions; RelayHealth; or the FDA.

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6. SURVEY PROCESS

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm prescriber eligibility. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, the respondent is immediately notified with a

"thank you" message that survey participation has ended. If eligible, the respondent is allowed to continue survey participation.

The data entry system used for both methods of survey administration has been validated and is secure for receiving and storing survey data. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Prescriber-identifying information will be stored separately from survey data.

6.1.1 Telephone

A trained interviewer from the Survey Coordinating Center will conduct the telephone interviews using a CATI program. The screening and main elements of the questionnaire will be administered sequentially during the same telephone call.

Telephone interviewing allows participation of prescribers who do not have Internet access. It will also be convenient for prescribers to participate since they can call in and be interviewed at their convenience during the specified time period when the Survey Coordinating Center is available.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If the prescriber selects to participate in the survey online, he/she will be directed to a secured website to complete screening questions. An Internet survey will be convenient for respondents to participate since they can complete the questionnaire at any time.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer the survey.

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All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. The data from the sample population will be reported using frequency distributions of responses to all questions.

The following will be reported as part of this analysis:

- The number of invitations issued to prescribers
- The number of reminder letters
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents eligible for participation who complete the survey
- Representativeness of prescribers based on geography
- Description of survey participants, including:
  - Gender
  - Medical degree of respondent: MD, DO, NP, PA
  - Medical specialty
  - Years of professional experience
  - How many times per month TIRF medicines prescribed in the last 6 months
  - Geographic region of practice

Additional descriptive statistics may be reported as appropriate.

7.1.1 Analysis Population

The analysis population will be based on eligible prescribers who completed all questions presented to them in the survey ("completers").

7.1.2 Description of Primary Analyses

Primary analyses are done for all key risk messages using data from all completers. The primary analysis for a key risk message evaluates the rate for each correct response to each individual question/item defined by the key risk message. The specific correct response to each question/item is identified in the body of the risk message table.

7.1.3 Description of Secondary Analyses

Secondary analyses are done only for those key risk messages that contain multiple questions/items using data from all completers. The secondary analysis entails a frequency distribution of the number of respondents who got 0, 1, etc. correct responses across the total number of items for the given key risk message.

8. SAFETY EVENT REPORTING

The term 'Safety Event' is defined as any information reported by a survey respondent that meets the criteria of an adverse event or product complaint. While it is not the intention of the survey to solicit the report of information that meets the criteria of a Safety Event, it is possible that a respondent may spontaneously report information that meets this criteria in free text fields of the survey (Internet-based administration) or while in conversation with the Survey Coordinating Center (telephone-based administration). The Internet-based questionnaires will be monitored for any comments recorded in the free text fields. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. Respondents will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact them if there are questions about the survey. Information on all reports (Internet or telephone) that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE PSP.

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9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The electronic data capture (EDC) system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail the $125 honorarium, a Thank You Letter, the correct responses to key risk messages, and the ISI after the survey is completed. Respondent contact information is also requested when necessary to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions in addition to instances where a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information (see Section 8 above).

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to prescribe TIRF medicines.

Appendix A Prescriber Questionnaire

Survey Legend

- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.

- **(INTERVIEWER)** is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by telephone only (for example, spontaneous adverse event reporting).

- **[ONLINE]** indicates a question is worded specifically for administering the survey online. **[PHONE]** indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.

- **[BEGIN ONLINE/PHONE SURVEY CONTENT]** and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.

- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

  Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.

- **[RANDOMIZE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as "I don't know," "Prefer not to answer" or "None of the above" will always appear at the end of the randomized responses.

- **[GO TO Qx]** (skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

- **[FREE TEXT]** indicates to the programmer that one line should be provided for data entry.

- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines).

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Survey Legend

- **[DROP-DOWN LIST INPUT WITH STATES TABLE]** indicates to the programmer that the response should be a drop-down list containing the states and US territories in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

- The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

Northeast Region

– New England Division - ME, NH, VT, MA, RI, CT
– Middle Atlantic Division - NY, NJ, PA

Midwest Region

– East North Central Division - OH, IN, IL, MI, WI
– West North Central Division - MN, IA, MO, ND, SD, NE, KS

South Region

– South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
– East South Central Division - KY, TN, AL, MS
– West South Central Division - AR, LA, OK, TX

Survey Legend

West

- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV
- Pacific Division WA, OR, CA, AK, HI

- The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

[BEGIN SURVEY CONTENT]

[ONLINE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess prescribers' understanding of the safe use and prescribing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc. The survey will take approximately 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to prescribe TIRF medicines.

How We Use Your Information

Your answers to the survey questions will be combined with answers given by other healthcare professionals taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $125 honorarium for your time and participation. This compensation represents the fair value for your services in connection with completion of the survey. The amount of the compensation was not determined in any manner that takes into account the volume or value of any referrals or business otherwise generated by you.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions. Physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your personal

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information will not be used in a manner inconsistent with this document. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

How to Learn More about This Survey

If you have questions about the survey, or problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Be sure to write down this telephone number; it will not be displayed again.

Taking the Survey

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

[PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess prescribers' understanding of the safe use and prescribing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." **(INTERVIEWER: Say "TIRF" then spell out T-I-R-F)** The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.);Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc; and Par Pharmaceutical, Inc. The survey will take approximately 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to prescribe TIRF medicines.

Now I would like to read some information about how your contact information will be used.

Your answers to the survey questions will be combined with answers given by other healthcare professionals taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $125 honorarium for your time and participation. This compensation represents the fair value for your services in connection with completion of the survey. The amount of the compensation was not determined in any manner that takes into account the volume or value of any referrals or business otherwise generated by you.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions. Physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

Now I would like to tell you some information about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your personal

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information will not be used in a manner inconsistent with this document. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

Now I will tell you how you can learn more about this survey. Please have a pen or pencil ready to write down a telephone number you can call if you have any questions about the survey. If you have questions about the survey, please ask me at any time. If you have questions at a later time, please contact the Survey Coordinating Center at 1-877-379-3297. Please feel free to ask me to repeat any questions or statements as we go through the survey. Once you have answered a question and moved on, we cannot go back and change your answers. Thank you for your participation in this survey.

[END PHONE PREAMBLE 1]

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[BEGIN INCLUSION/EXCLUSION QUESTIONS]

1. Your agreement to participate in this survey confirms mutual understanding in connection with completion of the survey and the fair market value of the payment to be rendered in connection with those services.

   Do you agree to participate in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

   - ○ Yes **[TERMINATE]**
   - ○ No
   - ○ I don't know **[TERMINATE]**

3. Are you enrolled in the TIRF REMS Access Program?

   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

4. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

   - □ Anesta LLC **[TERMINATE]**
   - □ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**
   - □ Depomed, Inc. **[TERMINATE]**
   - □ Galena Biopharma, Inc. **[TERMINATE]**
   - □ Insys Therapeutics **[TERMINATE]**

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- ☐ Mallinckrodt Pharmaceuticals **[TERMINATE]**
- ☐ McKesson Specialty Care Solutions **[TERMINATE]**
- ☐ Meda Pharmaceuticals **[TERMINATE]**
- ☐ Mylan, Inc. **[TERMINATE]**
- ☐ Par Pharmaceutical, Inc. **[TERMINATE]**
- ☐ RelayHealth **[TERMINATE]**
- ☐ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- ☐ United BioSource Corporation **[TERMINATE]**
- ☐ FDA **[TERMINATE]**
- ☐ None of these apply **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- ☐ I don't know **[TERMINATE]**
- ☐ Prefer not to answer **[TERMINATE]**

[END INCLUSION/EXCLUSION QUESTIONS]

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5. Please select True, False, or I don't know for each of the following.

According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:

[RANDOMIZE LIST]	True	False	I don't know
5a. Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	○	○	○
5b. Who are not currently taking opioid therapy, but have taken opioid therapy before	○	○	○
5c. Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	○	○	○

6. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

[RANDOMIZE LIST]	True	False	I don't know
6a. A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time.	○	○	○
6b. A cancer patient who has been on an around-the-clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.	○	○	○

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7. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
7a.	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	○	○	○
7b.	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	○	○	○
7c.	TIRF medicines may be used to treat opioid non-tolerant patients.	○	○	○
7d.	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	○	○	○
7e.	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	○	○	○

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8. Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
8a.	A personal history of psychiatric illness	○	○	○
8b.	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	○	○	○
8c.	A family history of asthma	○	○	○

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9. In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.

[RANDOMIZE LIST]	Yes	No	I don't know
9a. Acute or postoperative pain	○	○	○
9b. Headache or migraine pain	○	○	○
9c. Dental pain	○	○	○
9d. Breakthrough pain from cancer	○	○	○
9e. Chronic non-cancer pain	○	○	○

10. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

[RANDOMIZE LIST]	True	False	I don't know
10a. TIRF medicines can be abused in a manner similar to other opioid agonists.	○	○	○
10b. TIRF medicines are interchangeable with each other regardless of route of administration.	○	○	○
10c. The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	○	○	○
10d. Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	○	○	○

11. Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:

[RANDOMIZE LIST]	True	False	I don't know
11a. 8 mg oral hydromorphone/day	○	○	○
11b. 60 mg oral morphine/day	○	○	○
11c. 30 mg oral oxycodone/day	○	○	○
11d. 25 mcg transdermal fentanyl/hour	○	○	○
11e. 25 mg oral oxymorphone/day	○	○	○
11f. An equianalgesic dose of another oral opioid	○	○	○

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12. How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.

[RANDOMIZE LIST]	Always	Only with the first prescription	Sometimes	Never	I don't know
12a. Ask patients (or their caregivers) about the presence of children in the home	○	○	○	○	○
12b. Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	○	○	○	○	○
12c. Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	○	○	○	○	○
12d. Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	○	○	○	○	○
12e. Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	○	○	○	○	○
12f. Give patients (or their caregivers) the Medication Guide for their TIRF medicine	○	○	○	○	○

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13. The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine?

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[RANDOMIZE LIST]

13a. ○ Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.

13b. ○ Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.

13c. ○ Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.

13d. ○ Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.

13e. ○ I don't know

14. A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.

[RANDOMIZE LIST]

14a. ○ The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.

14b. ○ The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.

14c. ○ Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.

14d. ○ The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.

14e. ○ I don't know.

15. A patient is starting titration with a TIRF medicine. What dose must they start with? Please select one option.

[RANDOMIZE LIST]

15a. ○ An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.

15b. ○ The dose that the prescriber believes is appropriate based on their clinical experience.

15c. ○ The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.

15d. ○ The median available dose.

15e. ○ I don't know.

16. A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do? Please pick the best option of the scenarios described.

[RANDOMIZE LIST]

16a. ○ Take another (identical) dose of the TIRF medicine immediately.

16b. ○ Take a dose of an alternative rescue medicine.

16c. ○ Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.

16d. ○ Double the dose and take immediately.

16e. ○ I don't know.

17. A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please pick the best option of the scenarios described.

[RANDOMIZE LIST]

17a. ○ The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.

17b. ○ Use of a TIRF medicine with a CYP3A4 inhibitor may require a dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.

17c. ○ There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.

17d. ○ The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

17e. ○ I don't know.

18. Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.

[RANDOMIZE LIST]	True	False	I don't know
18a. TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.	○	○	○
18b. Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.	○	○	○
18c. Instruct patients that, if they stop taking their around-the-clock opioid medicine, they can continue to take their TIRF medicine.	○	○	○
18d. Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.	○	○	○

19. Can patients continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine?

- ○ Yes
- ○ No
- ○ I don't know

[PREAMBLE 2]

The next set of questions is about the educational materials for TIRF medicines and the TIRF Patient-Prescriber Agreement. As a reminder, the TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and generic versions of any of these brands.

20. Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you prescribe?

- ○ Yes
- ○ No **[GO TO Q22]**
- ○ I don't know **[GO TO Q22]**

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21. Did you read the Full Prescribing Information for the TIRF medicine(s) that you prescribe?

- Yes
- No
- I don't know

22. Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you prescribe?

- Yes
- No **[GO TO Q24]**
- I don't know **[GO TO Q24]**

23. Did you read the Medication Guide for the TIRF medicine(s) that you prescribe?

- Yes
- No
- I don't know

24. Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?

- Yes
- No **[GO TO Q26]**
- I don't know **[GO TO Q26]**

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25. What are your questions? **[MULTILINE INPUT]**

26. Do you review the Patient-Prescriber Agreement Form with each of your patients for whom you prescribe TIRF medicines or their caregiver?

- ○ Yes
- ○ No **[GO TO Q28]**
- ○ I don't know **[GO TO Q28]**

27. Do you and the patient or their caregiver sign the Patient-Prescriber Agreement Form for TIRF medicines after you have reviewed it with him/her?

- ○ Yes
- ○ No
- ○ I don't know

28. Do you give a copy of the Patient-Prescriber Agreement Form for TIRF medicines to the patient or their caregiver?

- ○ Yes
- ○ No
- ○ I don't know

[DEMOGRAPHICS PREAMBLE 1]

There are just a few more questions to help us combine your answers with other answers we have received.

29. On average, how many times per month have you prescribed the TIRF medicines within the last 6 months?

- ○ None **[GO TO DEMOGRAPHICS PREAMBLE 2]**
- ○ 1 – 2 times per month
- ○ 3 – 5 times per month
- ○ More than 5 times per month
- ○ I don't remember

30. Please select the TIRF medicines that you have prescribed within the last 6 months. Please select all that apply.

- ☐ Abstral®
- ☐ Actiq® or generic Actiq®
- ☐ Fentora®
- ☐ Lazanda®
- ☐ Onsolis®
- ☐ Subsys®

[DEMOGRAPHICS PREAMBLE 2]

These last few questions are for demographic purposes.

31. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

32. What is your medical degree?

- ○ MD
- ○ DO
- ○ Nurse Practitioner
- ○ Physician Assistant
- ○ Prefer not to answer

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33. In total, how many years have you been practicing medicine, since completing your education?

- ○ Less than 3 years
- ○ 3 – 5 years
- ○ 6 – 10 years
- ○ 11 – 15 years
- ○ More than 15 years
- ○ Prefer not to answer

34. In which state do you practice?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" at END]

35. What is your medical specialty?

- ○ Oncology
- ○ Primary care
- ○ Pain management
- ○ Other (please specify): **[FREE TEXT]**
- ○ No designated specialty

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[PHONE ONLY: BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- ○ Yes
- ○ No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[CLOSING 1]

We would like to send you a $125 honorarium within the next few weeks to thank you for your time, but we need your name and address to do so. If you do not provide your name and address you will not receive the honorarium for your time and participation in the survey. As a reminder, physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion.

Do you agree to give us your name and mailing address so we can send you the honorarium?

- ○ Yes
- ○ No **[SKIP TO CLOSING 2]**

FIRST NAME: **[FREE TEXT]**

LAST NAME: **[FREE TEXT]**

ADDRESS: **[MULTILINE INPUT]**

CITY: **[FREE TEXT]**

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: **[5 NUMERIC CHARACTERS ONLY]**

[CLOSING 2]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

Do you want to provide your telephone number?

- ○ Yes
- ○ No **[SKIP TO CLOSING 3]**

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[END CLOSING 2]

[CLOSING 3]

That ends the survey. Thank you again for your help.

[END OF SURVEY CONTENT]

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Appendix B SAMPLE Prescriber Invitation Letter

[CURR_DATE]

[PRESCRIBER NAME]

[STREET_ADDR]

[CITY], [STATE] [ZIP]

Dear [PRESCRIBER NAME]:

You were selected to receive this letter because you have enrolled in the TIRF REMS Access Program. We are contacting you to invite you to participate in a survey being conducted by the manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines, as required by the Food and Drug Administration (FDA). The purpose of the survey is to assess prescribers' understanding of the safe and appropriate use of these medicines. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

The manufacturers of TIRF medicines (collectively referred to as the "TIRF REMS Industry Group") include Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics; Mallinckrodt Pharmaceuticals; Meda Pharmaceuticals; Mylan, Inc., and Par Pharmaceutical, Inc. These manufacturers are looking for 300 prescribers to complete the survey. Eligible prescribers who complete the survey will be sent a $125 honorarium to thank them for their time. The survey will take 15-20 minutes.

Your answers will be kept strictly confidential and will be combined with the answers from other prescribers who take this survey. Your name will not be used in the report of this survey and your contact information will only be used to send you a $125 honorarium for the time you took to complete the survey and if required to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions. Prescribers who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

You are under no obligation to participate in this survey. If you are interested in participating, go to **www.XXXXXXXXXX.com** anytime or call **1-877-379-3297,** 8AM to 8PM Eastern Time Monday through Friday. You will be asked to give this unique code prior to starting the survey: **[CODE_ID]**.

Please have this letter with you at the time you take the survey. Thank you in advance for your help with this important effort.

Sincerely,

* We recommend that you take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.

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Moved up [1]: Please have this letter with you at the time you take the survey Thank you in advance for your help with this important effort ¶
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Appendix C Qualitative Research Report¶

The TIRF REMS Survey Team
1-877-379-3297
www.TIRFREMSsurvey.com

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