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September 18, 2013

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: 0005

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.

As agreed upon during the Agency's teleconference held on July 31, 2013, the final historical document for the REMS Assessment 2 at 12 months would be submitted as a separate sequence (0005).

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 610-535-6500, ext. 5572 or alternatively via email at jann.a.kochel@accenture.com.

Sincerely,

Jann A. Kochel

Jann A. Kochel, U.S. Agent
Accenture, LLP
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Wayne, PA 19087

Attachments: Table of Contents for the submission
Electronic Submission Specifications

Assessment – 12 Months

Module Section	Description
1.2 Cover Letter	Cover Letter w/ Attachments Administrative Information Page
1.16 – Risk Management Plans	REMS History REMS Assessment – 12 Months

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	09/11/2013 rev. 4
Submission Size	Approx. 1 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
2	Approval Pending	Draft Documents submitted on or before	**Sequence 0004:** Modification proposed to:

		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	• 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

Title: Transmucosal Immediate Release Fentanyl (TIRF)
Risk Evaluation and Mitigation Strategy (REMS) Access Program
12-month Assessment Report

Document Number: Final Version 1.0

Product Name: Transmucosal Immediate Release Fentanyl

Sponsor: TIRF REMS Industry Group (TRIG) of Companies:

Archimedes Pharma US Inc.
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)
Insys Therapeutics Inc.
Meda Pharmaceuticals
Mallinckrodt Inc. (the Pharmaceuticals Business of Covidien)
Par Pharmaceutical, Inc.
ProStrakan, Inc.

Confidentiality Statement

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LIST OF ABBREVIATIONS

AAPCC	American Association of Poison Control Centers
AERS	Adverse Event Reporting System
BTP	Breakthrough Pain
CSR	Center Service Representative
DEA	Drug Enforcement Administration
ETASU	Elements to Assure Safe Use
KAB	Knowledge, Attitude, and Behavior
FDA	Food and Drug Administration
MedDRA	Medical Dictionary for Drug Regulatory Activities
NCPDP	National Council for Prescription Drug Program
NDC	National Drug Code
NPI	National Provider Identifier
NCRT	Non-Compliance Review Team
PMS	Pharmacy Management System
PPAF	Patient-Prescriber Agreement Form
REMS	Risk Evaluation and Mitigation Strategy
REMS edits	Checks conducted by the TIRF REMS Access program to confirm that all safety requirements were met
SMQ	Standardized MedDRA Query
SOP	Standard Operating Procedure
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

EXECUTIVE SUMMARY

The Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation Mitigation Strategy (REMS) Access program was approved by the Food and Drug Administration (FDA) on 28 December 2011 for ABSTRAL®, ACTIQ®, FENTORA®, LAZANDA®, ONSOLIS® and generic versions of these TIRF medicines. On 04 January 2012, the FDA approved the inclusion of SUBSYS® to the TIRF REMS Access program. The TIRF REMS Access program was successfully launched on 12 March 2012, approximately 11 weeks after REMS approval. The initial REMS Assessment report was submitted on 28 June 2012 (cut-off date of 27 April 2012). This second REMS Assessment report covers the period from 27 April 2012 to 28 October 2012.

Upon launch of the TIRF REMS Access program, stakeholders (distributors, pharmacies, and prescribers) that had been enrolled in an individual REMS program were transitioned to the TIRF REMS Access program. The opportunity to transition into the TIRF REMS Access program from an individual REMS program ended on 12 September 2012.

There were no new "Dear Healthcare Professional Letter" mailings in this reporting period; however, 42 letters were returned that had been mailed during the initial reporting period including 7 Dear Healthcare Professional letters and 35 Pharmacist letters (33 outpatient and 2 inpatient pharmacies).

Stakeholder enrollment (transitioned and newly enrolled) in the TIRF REMS Access program during the current reporting period included 1,862 prescribers and 2,595 pharmacies. No wholesaler/distributors enrolled during the current reporting period. Additionally, 4,290 patients were enrolled who had prescription activity during the current reporting period. Implementation of the TIRF REMS Access program for closed system pharmacies (integrated healthcare systems with outpatient pharmacy management systems [PMS] unable to support the electronic transmission for required validation and claims), was launched on 30 June 2012.

No wholesalers/distributors were inactivated during the reporting period. A total of 6 pharmacies were inactivated due to opting out of the TIRF REMS Access program (2 inpatient, 33.3%; 4 outpatient, 66.7%). A total of 445 prescribers were inactivated with 98.7% due to expiration of enrollment period.

There were 143 incomplete prescriber enrollment forms received. The majority of incomplete forms were incomplete due to missing physician signature date (45.5%), missing signature (45.5%), and missing e-mail (18.2%).

There were 61 incomplete pharmacy enrollments attempts via fax, mostly due to invalid Drug Enforcement Administration (DEA) number (4.9%), missing DEA number (3.3%), invalid National Provider Identifier (NPI; 1.6%), invalid National Council for Prescription Drug Program (NCPDP; 1.6%), and missing state license number (1.6%).

Of 658 outpatient pharmacies that attempted to configure a PMS, 96.5% successfully configured their systems in a mean of 2.49 days (min/max; 0.0002 days/189.97 days).

A total of 54,614 prescriptions were adjudicated for safety by the TIRF REMS Access program and 96.3% of those prescriptions were subsequently approved for dispensing. There were 505 patients who had 3 or more prescribers in a rolling 6-month period. Patients may have multiple prescribers for various reasons such as patient relocation, prescriber relocation/retirement/death, or patient is seen at a single practice with multiple prescribers.

A total of 7,444 prescriptions were dispensed to 4,244 patients during the first 10 days after patient enrollment (i.e., enrollment occurred when first prescription was filled). There were a greater number of patients who had their first prescription filled in the first 10 days without a Patient-Prescriber Agreement Form (PPAF) compared with those patients with a PPAF (71.4% vs. 14.2%). For patients without a PPAF, the majority of patients (80.0%) received only 1 fill.

A total of 11,313 prescription claims were rejected because the claim failed to meet REMS requirements for prescriber and/or patient and/or pharmacy. A single prescription may have been submitted and rejected multiple times. The majority of rejection reasons were due to prescriber not enrolled or prescriber ID entered was not found in the TIRF REMS Access database (44.8%), PPAF incomplete (22.2%), patient zip code missing from claim (17.3%), prescriber last name did not match name registered (15.2%), and pharmacy not enrolled (8.3%).

The TIRF REMS Access program Call Center was contacted most frequently for the following reasons: pharmacy:pharmacy claim rejection (15.1%), enrollment status inquiry (14.1%), prescriber:pharmacy claim rejection (11.7%), PPAF follow up or status inquiry (20.9%).

There were no reports from patients of inability to find an enrolled pharmacy. There were no reports from patients of an inability to find an enrolled prescriber. No reports of inadvertent enrollment deactivations were identified; 2 reports concerning confirmed or potential non-compliant activity; and 7 issues were identified as system errors.

During the current reporting period, 36 FDA Adverse Event Reporting System (AERS) case reports in the United States (US) were associated with a TIRF medicine exposure. Twenty-seven (27) of the cases included one of the individual Preferred Terms (PT) of Interest for the TIRF REMS or at least one PT from the Medical Dictionary for Drug Regulatory Activities (MedDRA) standardized MedDRA Query (SMQ), *Acute Central Respiratory Depression*.

There were 11 cases of exposure to known oral fentanyl immediate-release medicines reported to the American Association of Poison Control Centers (AAPCC) during the current reporting period. No deaths were reported for exposures to TIRF medicines. There were 3 pediatric exposures reported for TIRF medicines, including 1 minor effect and 1 no effect in children <6 years of age, and a moderate effect in a teenager who was 13 to 19 years of age.

Twelve cases of exposure to unknown fentanyl were reported to the AAPCC during the current reporting period. The cases had medical outcomes of 7 deaths (indirect reports), 2 moderate effects, 1 minor effect, 1 unable to follow/judged as potentially toxic exposure, and 1 no effect. There were no pediatric exposures.

The patient Knowledge, Attitude, and Behavior (KAB) survey showed that the ongoing patient-oriented educational process is meeting its objectives in that the majority of patients completing the survey were aware of the key safety issues related to their use of a TIRF medication.

In the prescriber and pharmacist KABs, a minority of prescribers and pharmacists correctly indicated that patients considered opioid tolerant are those who are taking regular opioid therapy for one week or longer (12.6% pharmacists and 7.9% prescribers). Few prescribers and pharmacists correctly indicated patients not currently taking opioid therapy but who have unknown intolerance or hypersensitivity to fentanyl are not considered opioid tolerant (15.6%, for prescribers and pharmacists). Because both pharmacists and prescribers had low correct response rates for both of these questions, and because the high correct response rates for the other related risk messages, including other questions about opioid tolerance, this may possibly indicate a challenge in understanding the questions and not a knowledge issue. Additional research will be conducted to explore these results. The outcome of the research will be included in the next assessment report, and, based on the outcome, appropriate action may be taken.

Across the surveys for all key risk messages both pharmacists and prescribers demonstrated a high level of understanding that TIRF medicines are contraindicated in opioid non-tolerant patients, are only indicated for the management of breakthrough pain in adult patients with cancer, contain fentanyl with abuse liability similar to other opioid analgesics, and are not interchangeable with each other regardless of route of administration.

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.

Transmucosal immediate release fentanyl products ("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.

Fentanyl, an opioid agonist and a Schedule II controlled substance, is approximately 100-fold more potent than morphine as an analgesic.[1] Secondary effects of fentanyl on central nervous system, respiratory and gastrointestinal functions are typical of opioid analgesics and are considered to be an effect.[2]

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 TIRF REMS Access program was approved by the FDA on 28 December 2011 for ABSTRAL, ACTIQ, FENTORA, LAZANDA, ONSOLIS and generic versions of these TIRF medicines. On 04 January 2012, the FDA approved the inclusion of SUBSYS to the TIRF REMS. The group of Sponsors that are submitting this REMS (Archimedes Pharma US Inc., Cephalon, Inc. [a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.], Insys Therapeutics Inc., Meda Pharmaceuticals, Mallinckrodt Inc. [the Pharmaceuticals Business of Covidien], Par Pharmaceutical, Inc., and ProStrakan, Inc.) are hereafter referred to as the TIRF Sponsors. At the time of protocol development for the Knowledge, Attitude, and Behavior (KAB) surveys, Sandoz was also a member of the group of TIRF Sponsors; however Sandoz

[1] Biedrzycki OJ, Bevan D, Lucas S, Fatal overdose due to prescription fentanyl patches in a patient with sickle cell/beta- thalassemia and acute chest syndrome: A case report and review of the literature. *Am J Forensic Med Pathol*. 2009 Jun; 30(2): 188-90

[2] Simpson DM, Messina J, Xie F, Hale M. Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther*. 2007 Apr; 29(4):588-601.

terminated their involvement in the TIRF REMS Access program, effective 15 September 2012. 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 citrate) 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 provided to TIRF Sponsors. The program will be monitored over time and modified when and where appropriate.

1.1 Reporting Period

The initial REMS was approved on 28 December 2011 and went live on 12 March 2012. FDA requires an initial report 6 months after initial approval; therefore, the first report was submitted on 28 June 2012 with a cut-off date of 27 April 2012. For this 12-month reporting period the cut-off date was 28 October 2012 thereby allowing 60 days to prepare this report for the FDA, which is due on 28 December 2012.

Data cutoffs include all data and information available from the start of the reporting period up to the end of each reporting period to allow for programming, analysis, and report writing. Reports are scheduled for completion according to the following schedule:

Reports	Reporting Interval	Date Sent to FDA
6 months REMS Assessment	12/28/2011 - 04/27/2012	06/28/2012
12 months REMS Assessment	04/28/2012 - 10/28/2012	12/28/2012
24 months REMS Assessment*	10/29/2012 - 10/28/2013	12/28/2013

***Annually thereafter**

2 REMS GOALS

The goals of the TIRF REMS Access program 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.

2.1 The TIRF REMS Access Program Transition Plan: From Individual to Shared REMS

Upon launch of the TIRF REMS Access program on 12 March 2012, all stakeholders (distributors, pharmacies, and prescribers) enrolled in an individual TIRF product REMS program were transitioned to the TIRF REMS Access program. From this point onward, all new stakeholders were required to enroll in the TIRF REMS Access program. Pharmacies enrolled in individual REMS programs were required to re-new their Terms & Conditions as part of enrolling in the TIRF REMS Access program. Pharmacies that did not complete this action by 12 September 2012 were not transitioned into the TIRF REMS Access program.

Metrics that include transitioned stakeholders are so noted within this report. As of 12 September 2012, all stakeholders were required to enroll in the TIRF REMS Access program and could no longer transition into the TIRF REMS Access program from individual REMS programs.

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, pharmacists and distributors must be enrolled in the TIRF program, educated on the requirements of the program and required to document that they understood and would abide by the “elements to assure safe use.”

Program materials are provided on the TIRF medicines in addition to product-specific materials. The Educational Program and Knowledge Assessment components of the program contain both TIRF medicine class and product-specific components. All program tools, including enrollment forms, PPAF, stakeholder letters, and overview documents containing program information specific to the TIRF REMS Access program, are available through the www.TIRFREMSACCESS.com Web site.

The program procedures are monitored for adherence and the TIRF Sponsors will continue to conduct ongoing and retrospective analysis 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 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. In this reporting period, there were no mailings of either the Dear Healthcare Provider or Dear Pharmacy letters.

3.2 Elements to Assure Safe Use (ETASU)

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 was achieved by 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 to be 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 were only dispensed to appropriate patients, pharmacies are enrolled into the TIRF REMS Access program. There was a different set of 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 were enrolled in the TIRF REMS Access program.

Implementation of the TIRF REMS Access program for closed system pharmacies was launched on 30 June 2012. Closed System Pharmacies are integrated healthcare systems that dispense for outpatient use with pharmacy management systems unable to support the process of electronically transmitting the validation and claim information required.

Outpatient pharmacy enrollment required an authorized pharmacist at the pharmacy to undergo enrollment through review of the TIRF REMS Access Education Program and successful

completion of the Knowledge Assessment on behalf of the pharmacy and submission of a completed and signed TIRF REMS Access program enrollment form. The authorized pharmacist ensured the pharmacy enabled their pharmacy management system (PMS) to support communication with the TIRF REMS Access program using established telecommunication standards. This required standardized validation test transactions to validate the system enhancements. The authorized pharmacist was responsible for educating all pharmacy staff who participated in dispensing TIRF medicines on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program. This training was to be documented and is subject to an audit.

For inpatient pharmacy enrollment, the authorized pharmacist underwent the TIRF REMS Access Education program, successfully completed the Knowledge Assessment, and submitted a completed and signed enrollment form on behalf of the pharmacy. The authorized inpatient pharmacist acknowledged that they understood that outpatient pharmacies within their facility were to be separately enrolled.

For chain pharmacies, an authorized chain pharmacy representative completed enrollment. The authorized chain pharmacy representative acknowledged that training would occur for all pharmacy staff involved in the dispensing of TIRF medicines. Once the TIRF REMS Access Education program and Knowledge Assessment were completed, the authorized chain pharmacy representative, on behalf of the chain, was required to acknowledge their understanding of the appropriate use of TIRF medicines and to agree to adhere to the TIRF REMS Access program requirements by submitting a completed and signed enrollment form.

Patients were enrolled in the TIRF REMS Access program when their first prescription was processed at the pharmacy. A completed PPAF needed to 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 three prescriptions were allowed within 10 working days from when the patient had their first prescription filled. No further prescriptions were dispensed after the 10 working day window until a completed PPAF was received. A patient's healthcare provider can submit a copy of the PPAF to the TIRF REMS Access program via the Web site, fax, or US mail. In some cases, a PPAF may never be received if the patient received only one prescription without a PPAF and never attempted to fill another prescription, or the patient subsequently died

3.2.1 Prescription Verification

Following initial patient enrollment on processing of a patient's first TIRF medicine prescription, pharmacies verified for all subsequent prescriptions that both the prescriber and patient were enrolled in the TIRF REMS Access program prior to dispensing. Prescription verification was not required for inpatient use of TIRF medicines.

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

On receipt of a prescription for a TIRF medicine at an enrolled pharmacy, the pharmacist entered the prescription details in their PMS and sent the transaction to the TIRF REMS Access

program via a switch provider. The TIRF REMS Access program used this transaction data to automatically transfer patient details into the TIRF REMS Access database for enrollment.

For all prescriptions, the REMS database was then interrogated, via the switch provider, to validate the REMS edits (i.e., met the TIRF REMS Access program requirements).

In the case of a valid prescription, a billing request was sent to the payer by the switch provider. Once the payer authorized payment the switch provider then authorized the pharmacy to dispense the TIRF medicine as with a normal prescription, returning an authorization number which was captured by the TIRF REMS Access program.

If the prescription was not valid (e.g. one of the stakeholders was not enrolled), the TIRF REMS Access program rejected the claim (prior to the claim being forwarded to the payer) and the pharmacy received a rejection notice from the switch provider. This automated feedback indicated the reason for rejection, instructed the pharmacist not to dispense the TIRF medicine, and notified the pharmacist to contact the TIRF REMS Access program Call Center for further information.

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. The distributor's authorized representative reviewed the distributor program materials. The distributor's authorized representative must complete and sign the Distributor Enrollment Form and faxed it to the TIRF REMS Access program. TIRF Sponsors did not ship TIRF medicines to any distributor who had not completed and signed the enrollment form.

3.3.2 The TIRF REMS Access Program Compliance

TIRF Sponsors monitored prescriber, inpatient and outpatient pharmacy, and wholesaler/distributor activities for compliance with TIRF REMS Access program requirements. Corrective action (e.g., re-education, additional monitoring, process revision, stakeholder inactivation) was instituted by the TIRF Sponsors as appropriate if noncompliance was found.

3.3.3 TIRF REMS Access Program Call Center

The TIRF REMS Access program included a Call Center component. The Call Center was staffed by qualified and trained specialists, who provided 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 was 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 were used in an effort to improve the processes, as needed.

4.1 Data Sources

Data were collected from the following main sources as described in detail below: a) the TIRF REMS Access program outreach (Section 4.1.1), b) TIRF REMS Access product and program utilization statistics (Section 4.1.2), c) program infrastructure and performance (Section 4.1.3), and d) safety surveillance (Section 4.1.4). All programmed source tables and histograms, 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 TIRF REMS Access Program Outreach

The following metrics were tabulated for this reporting period to assess program outreach efforts (Section 5.1.1):

1. Number of Dear HCP letters mailed to prescribers (by date)
2. Number of returned mailings of Dear HCP letters to prescribers.
3. Number of Pharmacist letters mailed to pharmacies (by date)
4. Number of returned mailings of Pharmacist letters to pharmacies

4.1.2 The TIRF REMS Access Program and Product Utilization Statistics

For the assessment of enrollment, utilization, and discontinuation statistics for prescribers, pharmacies, patients, and wholesalers, the following metrics were tabulated for this reporting period and cumulatively:

5. Number of new patients enrolled by state (Section 5.2.1)
6. Number of patients inactivated (Section 5.2.1)
7. Number of attempts needed for prescribers to successfully complete Knowledge Assessments (Section 5.2.2)
    - Method of completion
8. Number of new prescribers enrolled by state (Section 5.2.2)
    - Method of enrollment

- Number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields

9. Number of prescribers who are inactivated (Section 5.2.2)
10. Number of new pharmacies enrolled by type (inpatient or outpatient), by state (Section 5.2.3)
    - Method of enrollment
    - Number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields
11. Number of pharmacies that are inactivated by type (inpatient or outpatient) (Section 5.2.3)
12. Number of attempts needed for pharmacies to successfully complete Knowledge Assessments (Section 5.2.3)
13. Dispensing activity for enrolled outpatient pharmacies (Section 5.2.4)
    - Total number of prescriptions authorized
    - Total number of prescriptions rejected for safety (description of safety issues and any interventions or corrective actions taken)
14. Summary of cases identified where a patient received prescriptions for a TIRF medicine from multiple prescribers within an overlapping time frame (description of any investigations and the outcome) (Section 5.2.4)
15. Number of wholesalers/distributors inactivated, total (Section 5.2.5)
16. Number of new wholesalers/distributors enrolled (Section 5.2.5)
    - Method of enrollment
    - Number of incomplete forms, to extent possible, a brief description of the reason for incomplete data fields
17. Number of days between enrollment and receipt of a PPAF (Section 5.2.6)
    - Method of PPAF submission
18. Number of prescriptions dispensed per patient during the first 10 days after patient enrollment with and without a PPAF in place. (Section 5.2.6)
    - A histogram of the number of days between passive enrollment and receipt of a PPAF. Stratify by the method of PPAF submission
    - A histogram of the number of prescriptions dispensed per patient during the first 10 days after patient passive enrollment stratified by whether there is a PPAF in place.

4.1.3 Program Infrastructure and Performance

The following metrics on program infrastructure performance were tabulated for this reporting period and cumulatively:

19. Assessment of process for pharmacies to upgrade their PMS (mean, maximum, and minimum time needed, number of pharmacies that attempted and failed to upgrade their systems) (Section 5.3.1)
20. Number of times a backup system was used to validate a prescription, with reason for each instance (pharmacy level problem, switch problem, or REMS database problem) (Section 5.3.2)
21. Call center report (Section 5.3.3)
    a. Summary of frequently asked questions
    b. Problems reported
22. Description of corrective actions taken to address program/system problems (Section 5.4)
23. Number of reports of lack of enrolled prescribers and/or pharmacies in a patient's area (Section 5.4.1)
24. Delays after original prescriptions are denied by pharmacy and brief summary to include characterization of delays (Section 5.4.2)

The following reports for unintended system interruptions were provided for this reporting period:

25. Reports identified of inadvertent enrollment deactivations (Section 5.5.1)
26. Reports of false positives (e.g., all entities not enrolled but system generated a prescription authorization code) (Section 5.5.2)
27. Reports of failure of re-enrollment notifications to reach stakeholders (Section 5.5.3)
28. Reports of false negatives (e.g., all entities enrolled but the system generated a prescription rejection notice), including brief summary of reason for rejection (Section 5.5.4)

4.1.4 Safety Surveillance

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

Surveillance data from the following sources are included in the REMS Assessment Reports:

- FDA adverse event reporting system (AERS) database using signal detection methods for TIRF medicines to identify outcomes of death, overdose, misuse, abuse, addiction, inappropriate prescribing, medication errors, and accidental exposures/ingestion period. See Appendix 11.1 for list of Medical Dictionary for Drug Regulatory Activities (MedDRA) Preferred Terms used.
- AAPCC (Appendix 11.2) data for TIRF medicines and unknown fentanyl products with inhalation or ingestion as routes of exposure.

4.2 TIRF REMS Access Program Non-Compliance Plan

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 ensure that TRIG monitors the functioning of TIRF REMS Access program and identifies and investigates deviations and non-compliance with TIRF REMS requirements in order to ensure patient safety and continuously improve the program. A TIRF REMS Access program Non-Compliance Review Team (NCRT) was created from the companies of the TRIG on 19 October 2012. The NCRT reviews reports of suspected non-compliance with respect to the TIRF REMS Access program requirements.

4.2.1 Corrective Action Measures

Stakeholders that fail to comply with one or more elements of the TIRF REMS Access program will be subject to corrective action. Corrective actions resulting from non-compliance will be determined by the TIRF REMS Access program according to the severity of the action.

5 RESULTS

5.1 TIRF REMS Access Program Outreach

5.1.1 Dear Healthcare Professional Letters [Metric 1-4]

There were no new mailings in this reporting period; however, 42 letters were returned that had been mailed during the previous reporting period including 7 Dear Healthcare Professional letters (Metric 2) and 35 Pharmacist letters (33 outpatient and 2 inpatient pharmacies; Metric 4).

5.2 REMS Program Utilization

Described below is the total number and geographic distribution of all enrolled stakeholders (prescribers, patients, distributors, outpatient independent and inpatient pharmacies, corporate chain pharmacy offices and chain pharmacy stores), as well as stakeholder enrollment and inactivations, dispensing activities, and barriers or delays in patient access.

5.2.1 Patient Enrollment [Metric 5 and 6]

During the current reporting period, there were 4,290 patients from 49 states (Vermont had no patients enrolled), the District of Columbia and Puerto Rico who were enrolled in the REMS program, i.e., they had prescription activity during the current reporting period (Table 2). The following states had the highest proportion of enrolled patients: California (10.4%), Florida (6.5%), Texas (6.4%), New York (4.1%), New Jersey (3.6%), Alabama (3.2%, and Pennsylvania (2.6%).

For 31.6% of patients, state/territory was unknown. Patients enrolled in the TIRF REMS Access program provide consent for data use in reporting then they sign the PPAF; therefore, location cannot be reported on enrolled patients who do not have a PPAF on file. For patients

who submitted more than one PPAF, the location is recorded from the first completed PPAF received.

There were no patients inactivated during the reporting period (not shown in Table 3; Data Sources: Table 6c: MCK_UBC_TIRF_FDA_Reporting_Enrollment_ Status_ History_110220121036.txt.

Table 2: Patient Enrollment and Geographic Distribution

	Current Reporting Period[a] 28APR2012 to 28OCT2012	**Cumulative[a,b] 28DEC2011 to 28OCT2012**
Parameter	**N (%)**	**N (%)**
Number of Newly Enrolled Patients[c]	4,290	12,071
State/Territory of Patient Primary Address[d]		
Unknown	1,357 (31.6%)	2,143 (17.8%)
Alabama	138 (3.2%)	237 (2.0%)
Alaska	6 (0.1%)	31 (0.3%)
Arizona	55 (1.3%)	187 (1.6%)
Arkansas	32 (0.8%)	63 (0.5%)
California	446 (10.4%)	1,507 (12.5%)
Colorado	66 (1.5%)	280 (2.3%)
Connecticut	39 (0.9%)	148 (1.2%)
Delaware	8 (0.2%)	52 (0.4%)
Florida	278 (6.5%)	898 (7.4%)
Georgia	80 (1.9%)	266 (2.2%)
Hawaii	3 (0.1%)	18 (0.2%)
Idaho	5 (0.1%)	24 (0.2%)
Illinois	72 (1.7%)	288 (2.4%)
Indiana	48 (1.1%)	176 (1.5%)
Iowa	6 (0.1%)	31 (0.3%)
Kansas	27 (0.6%)	97 (0.8%)
Kentucky	17 (0.4%)	75 (0.6%)
Louisiana	16 (0.4%)	52 (0.4%)
Maine	1 (<0.1%)	12 (0.1%)
Maryland	56 (1.3%)	222 (1.8%)
Massachusetts	30 (0.7%)	95 (0.8%)
Michigan	100 (2.3%)	322 (2.7%)

(continued)

Table 2: Patient Enrollment and Geographic Distribution

	Current Reporting Period[a] 28APR2012 to 28OCT2012	Cumulative[a,b] 28DEC2011 to 28OCT2012
Parameter	**N (%)**	**N (%)**
Minnesota	7 (0.2%)	34 (0.3%)
Mississippi	26 (0.6%)	54 (0.5%)
Missouri	47 (1.1%)	133 (1.1%)
Montana	5 (0.1%)	17 (0.1%)
Nebraska	8 (0.2%)	32 (0.3%)
Nevada	20 (0.5%)	84 (0.7%)
New Hampshire	3 (0.1%)	25 (0.2%)
New Jersey	153 (3.6%)	654 (5.4%)
New Mexico	1 (<0.1%)	16 (0.1%)
New York	177 (4.1%)	619 (5.1%)
North Carolina	91 (2.1%)	313 (2.6%)
North Dakota	2 (0.1%)	12 (0.1%)
Ohio	86 (2.0%)	268 (2.2%)
Oklahoma	43 (1.0%)	156 (1.3%)
Oregon	16 (0.4%)	82 (0.7%)
Pennsylvania	113 (2.6%)	407 (3.4%)
Rhode Island	15 (0.4%)	36 (0.3%)
South Carolina	41 (1.0%)	108 (0.9%)
South Dakota	1 (<0.1%)	4 (<0.1%)
Tennessee	60 (1.4%)	216 (1.8%)
Texas	273 (6.4%)	866 (7.2%)
Utah	67 (1.6%)	192 (1.6%)
Vermont	0	1 (<0.1%)
Virginia	46 (1.1%)	184 (1.5%)
Washington	75 (1.8%)	198 (1.6%)
West Virginia	4 (0.1%)	33 (0.3%)
Wisconsin	10 (0.2%)	66 (0.6%)
Wyoming	11 (0.3%)	30 (0.3%)

(continued)

Table 2: Patient Enrollment and Geographic Distribution

	Current Reporting Period[a] 28APR2012 to 28OCT2012	Cumulative[a,b] 28DEC2011 to 28OCT2012
Parameter	**N (%)**	**N (%)**
District of Columbia	2 (0.1%)	5 (<0.1%)
Guam	0	0
Puerto Rico	1 (<0.1%)	2 (<0.1%)
Virgin Islands	0	0

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

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

[c] Patients enrolled in this time period and were still enrolled at the end of the time period.

[d] Patients are classified by state based on 5-digit zip code provided on PPAF. If the zip code is invalid, the patient's self-reported state is used if available.

Data Source: Table 1 c: MCK UBC TIRF FDA Reporting Enrollment 110220121036.txt
MCK_UBC_TIRF_FDA_Reporting_Patient_111420121036.txt

Based upon FDA request, this report includes the proportion of states' populations enrolled as a TIRF REMS patient, as calculated using the number of new patients in that state divided by the total population of that state as per the latest US census data. The number of newly enrolled patients in the TIRF REMS Access program is shown in the table below for the reporting period from 28 April 2012 to 28 October 2012 and cumulatively from 28 April 2012 to 28 October 2012. In addition, the proportion of these patients enrolled by state population using data from the United States Census of 2010 is presented (Table 3).

The highest proportion of patients enrolled according to state population were in the states of New Jersey (0.0074%), Utah (0.0069%), Delaware (0.0058%), Colorado (0.0056%), Wyoming (0.0053%), Alabama (0.0050%), and Florida (0.0048%).

Table 3: Patient Enrollment by State According to 2010 US Census

State\Territory of Patient Primary Address[a]	Current Reporting Period 28APR2012 to 28OCT2012[b]	Cumulative 28DEC2011 to 28OCT2012[b]	Population Derived from 2010 US Census Data[c]	Percentage of Population Enrolled in TIRF REMS Access[d]	Rate of Persons Enrolled (Per 100,000)[d]
Total	4,290	12,071	312,471,327	0.00004%	0.04
Unknown	1,357	2,143	N/A	N/A	N/A
Alabama	138	237	4,779,736	0.0050%	5.0
Alaska	6	31	710,231	0.0044%	4.4
Arizona	55	187	6,392,017	0.0029%	2.9
Arkansas	32	63	2,915,918	0.0022%	2.2
California	446	1,507	37,253,956	0.0040%	4.0
Colorado	66	280	5,029,196	0.0056%	5.6
Connecticut	39	148	3,574,097	0.0041%	4.1
Delaware	8	52	897,934	0.0058%	5.8
Florida	278	898	18,801,310	0.0048%	4.8
Georgia	80	266	9,687,653	0.0027%	2.7
Hawaii	3	18	1,360,301	0.0013%	1.3
Idaho	5	24	1,567,582	0.0015%	1.5
Illinois	72	288	12,830,632	0.0022%	2.2
Indiana	48	176	6,483,802	0.0027%	2.7
Iowa	6	31	3,046,355	0.0010%	1.0
Kansas	27	97	2,853,118	0.0034%	3.4
Kentucky	17	75	4,339,367	0.0017%	1.7
Louisiana	16	52	4,533,372	0.0011%	1.1
Maine	1	12	1,328,361	0.0009%	0.9

(continued)

Table 3: Patient Enrollment by State According to 2010 US Census

State\Territory of Patient Primary Address[a]	Current Reporting Period 28APR2012 to 28OCT2012[b]	Cumulative 28DEC2011 to 28OCT2012[b]	Population Derived from 2010 US Census Data[c]	Percentage of Population Enrolled in TIRF REMS Access[d]	Rate of Persons Enrolled (Per 100,000)[d]
Maryland	56	222	5,773,552	0.0038%	3.8
Massachusetts	30	95	6,547,629	0.0015%	1.5
Michigan	100	322	9,883,640	0.0033%	3.3
Minnesota	7	34	5,303,925	0.0006%	0.6
Mississippi	26	54	2,967,297	0.0018%	1.8
Missouri	47	133	5,988,927	0.0022%	2.2
Montana	5	17	989,415	0.0017%	1.7
Nebraska	8	32	1,826,341	0.0018%	1.8
Nevada	20	84	2,700,551	0.0031%	3.1
New Hampshire	3	25	1,316,470	0.0019%	1.9
New Jersey	153	654	8,791,894	0.0074%	7.4
New Mexico	1	16	2,059,179	0.0008%	0.8
New York	177	619	19,378,102	0.0032%	3.2
North Carolina	91	313	9,535,483	0.0033%	3.3
North Dakota	2	12	672,591	0.0018%	1.8
Ohio	86	268	11,536,504	0.0023%	2.3
Oklahoma	43	156	3,751,351	0.0042%	4.2
Oregon	16	82	3,831,074	0.0021%	2.1
Pennsylvania	113	407	12,702,379	0.0032%	3.2
Rhode Island	15	36	1,052,567	0.0034%	3.4
South Carolina	41	108	4,625,364	0.0023%	2.3
South Dakota	1	4	814,180	0.0005%	0.5

(continued)

Table 3: Patient Enrollment by State According to 2010 US Census

State\Territory of Patient Primary Address[a]	Current Reporting Period 28APR2012 to 28OCT2012[b]	Cumulative 28DEC2011 to 28OCT2012[b]	Population Derived from 2010 US Census Data[c]	Percentage of Population Enrolled in TIRF REMS Access[d]	Rate of Persons Enrolled (Per 100,000)[d]
Tennessee	60	216	6,346,105	0.0034%	3.4
Texas	273	866	25,145,561	0.0034%	3.4
Utah	67	192	2,763,885	0.0069%	6.9
Vermont	0	1	625,741	0.0002%	0.2
Virginia	46	184	8,001,024	0.0023%	2.3
Washington	75	198	6,724,540	0.0029%	2.9
West Virginia	4	33	1,852,994	0.0018%	1.8
Wisconsin	10	66	5,686,986	0.0012%	1.2
Wyoming	11	30	563,626	0.0053%	5.3
District of Columbia	2	5	601,723	0.0008%	0.8
Puerto Rico	1	2	3,725,789	0.0001%	0.1

N/A = not applicable

[a] Patients are classified by state based on 5-digit zip code provided on PPAF.

[b] Patients enrolled in this time period and were still enrolled at the end of the time period.

[c] Based on 2010 US Census Data

[d] Rates are based on Cumulative enrollment.

Source: Table 1.e: MCK_UBC_TIRF_FDA_Reporting_Enrollment_110220121036.txt
MCK_UBC_TIRF_FDA_Reporting_Patient_111420121036.txt

5.2.2 Prescriber Enrollment, Inactivation, and Education [Metric 7, 8, 9]

During the current reporting period, there were 1,862 prescribers from all 50 states, the District of Columbia, and Puerto Rico who were newly enrolled in the TIRF REMS Access program (Table 4).

The majority of these enrolled prescribers (86.5%) enrolled using the Web-based enrollment system. Almost all the other prescribers completed their enrollment manually and submitted it by fax (13.4%). One prescriber (0.1%) who previously transitioned into the TIRF REMS Access program with an incomplete enrollment subsequently completed enrollment during the current reporting period. This prescriber appears as "one-time file upload" (i.e., transitioned from other individual REMS programs) in the table below.

The highest enrolling state was California (14.7%), followed by New York (8.2%), Texas (7.9%), Pennsylvania (5.9%), and Florida (5.3%); all other states had enrollment of ≤4.3%.

There were 143 incomplete prescriber enrollment forms received for prescribers who enrolled via fax. Multiple forms may have been submitted for the same prescriber, and a form may be incomplete for more than one reason. The majority of incomplete forms were incomplete due to missing physician signature date (45.5%), missing signature (45.5%), missing e-mail (18.2%), invalid DEA number (5.6%), and DEA number did not have correct schedule for drug (4.9%).

Prescribers who enroll via Web do not submit forms. They move through a series of enrollment modules and, at any given time in the process, one or more modules may be incomplete. A prescriber cannot enroll via Web unless all modules and requirements are completed. Of 339 prescribers who initiated enrollment via the Web and had not completed enrollment as of the last date of the current reporting period (28 October 2012; data on file), the reasons for incomplete enrollment that represented at least 80.0% of those enrolling via Web were no attestation (292, 86.14%) and training not complete (270, 79.65%).

Table 4: Prescriber Enrollment

	Current Reporting Period[a] 28APR2012 to 28OCT2012	**Cumulative[a,b] 28DEC2011 to 28OCT012**
Parameter	**N (%)**	**N (%)**
Number of Newly Enrolled Prescribers[c]	1,862[d]	8,115[d]
Method of Successful New Enrollments[e]		
Web	1,611 (86.5%)	3,881 (47.8%)
Fax	250 (13.4%)	396 (4.9%)
One-time file upload	1 (0.1%)	3,838 (47.3%)
State/Territory of Prescriber Primary Address[f]		
Alabama	13 (0.7%)	108 (1.3%)
Alaska	5 (0.3%)	20 (0.3%)
Arizona	56 (3.0%)	247 (3.0%)
Arkansas	13 (0.7%)	59 (0.7%)
California	274 (14.7%)	1,015 (12.5%)
Colorado	44 (2.4%)	188 (2.3%)
Connecticut	22 (1.2%)	109 (1.3%)
Delaware	8 (0.4%)	28 (0.4%)
Florida	98 (5.3%)	501 (6.2%)
Georgia	31 (1.7%)	189 (2.3%)
Hawaii	4 (0.2%)	14 (0.2%)
Idaho	8 (0.4%)	19 (0.2%)
Illinois	80 (4.3%)	290 (3.6%)
Indiana	30 (1.6%)	220 (2.7%)
Iowa	9 (0.5%)	26 (0.3%)
Kansas	10 (0.5%)	59 (0.7%)
Kentucky	12 (0.6%)	64 (0.8%)
Louisiana	13 (0.7%)	81 (1.0%)
Maine	3 (0.2%)	19 (0.2%)
Maryland	58 (3.1%)	283 (3.5%)
Massachusetts	45 (2.4%)	139 (1.7%)
Michigan	48 (2.6%)	208 (2.6%)
Minnesota	18 (1.0%)	79 (1.0%)
Mississippi	7 (0.4%)	36 (0.4%)

(continued)

Table 4: Prescriber Enrollment

	Current Reporting Period[a] 28APR2012 to 28OCT2012	Cumulative[a,b] 28DEC2011 to 28OCT012
Parameter	**N (%)**	**N (%)**
Missouri	26 (1.4%)	116 (1.4%)
Montana	3 (0.2%)	18 (0.2%)
Nebraska	26 (1.4%)	54 (0.7%)
Nevada	26 (1.4%)	70 (0.9%)
New Hampshire	6 (0.3%)	30 (0.4%)
New Jersey	54 (2.9%)	428 (5.3%)
New Mexico	8 (0.4%)	24 (0.3%)
New York	153 (8.2%)	540 (6.7%)
North Carolina	59 (3.2%)	318 (3.9%)
North Dakota	4 (0.2%)	11 (0.1%)
Ohio	37 (2.0%)	242 (3.0%)
Oklahoma	14 (0.8%)	82 (1.0%)
Oregon	26 (1.4%)	88 (1.1%)
Pennsylvania	109 (5.9%)	482 (5.9%)
Rhode Island	3 (0.2%)	16 (0.2%)
South Carolina	21 (1.1%)	77 (1.0%)
South Dakota	2 (0.1%)	6 (0.1%)
Tennessee	44 (2.4%)	240 (3.0%)
Texas	147 (7.9%)	573 (7.1%)
Utah	25 (1.3%)	123 (1.5%)
Vermont	2 (0.1%)	6 (0.1%)
Virginia	32 (1.7%)	195 (2.4%)
Washington	77 (4.1%)	200 (2.5%)
West Virginia	3 (0.2%)	30 (0.4%)
Wisconsin	28 (1.5%)	113 (1.4%)
Wyoming	8 (0.4%)	13 (0.2%)
District of Columbia	9 (0.5%)	17 (0.2%)
Guam	0	0
Puerto Rico	1 (0.1%)	2 (0.0%)
Virgin Islands	0	0

(continued)

Table 4: Prescriber Enrollment

	Current Reporting Period[a] 28APR2012 to 28OCT2012	Cumulative[a,b] 28DEC2011 to 28OCT012
Parameter	**N (%)**	**N (%)**
Distribution of Reasons for Incomplete Prescriber Enrollment Forms Received for Fax-Enrolled Prescribers[g, h]	143[i]	203[i]
Missing Physician Signature Date	65 (45.5%)	120 (59.1%)
Missing Signature	65 (45.5%)	120 (59.1%)
Missing Email	26 (18.2%)	50 (24.6%)
Invalid DEA Number	8 (5.6%)	29 (14.3%)
Provided DEA Number does not have Correct Schedule for this Drug	7 (4.9%)	28 (13.8%)
Invalid NPI Number	9 (6.3%)	20 (9.9%)
Missing State Medical License Number	11 (7.7%)	18 (8.9%)
Missing NPI Number	5 (3.5%)	12 (5.9%)
Missing DEA Number	5 (3.5%)	8 (3.9%)
Missing Fax Number	3 (2.1%)	4 (2.0%)

Note: Percentages are based on the total number (N) of prescribers for the period except for counts of incomplete forms.

[a] The table reflects only enrolled prescribers who completed enrollment via fax.

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

[c] Prescribers enrolled in this time period and still enrolled at the end of the time period. *New Prescriber* is defined as having passed Knowledge Assessment and completed enrollment form and does not include prescriber re-enrollments.

[d] Includes prescribers who transitioned into the TIRF REMS Access program from other individual REMS programs.

[e] Percentage is based on the number of prescribers new to the TIRF REMS Access program, including prescribers that transitioned from other individual REMS programs.

[f] Enrolled prescribers are classified by their primary address as recorded on the Prescriber Enrollment Form.

[g] Percentage is based on the total number of incomplete forms received in the reporting period. Forms may be incomplete for more than one reason and more than one incomplete form received for a unique prescriber.

[h] Reflects only enrolled prescribers who completed enrollment via fax. Some stakeholders may have attempted enrollment via the Web.

[i] Does not include prescribers who transitioned into the TIRF REMS Access program from other individual REMS programs.

Data Sources: Table 1a: MCK_UBC_TIRF_FDA_Prescriber_Location_110220121036.txt
MCK_UBC_TIRF_FDA_Reporting_Enrollment_Status_History_110220121036.txt

A total of 445 prescribers were inactivated at some point during the current reporting period, and the majority (439, 98.7%) was due to expiration of enrollment period. Of those 439 prescribers whose enrollment period expired at some point during the current reporting period, 409 (93.2%) of these prescribers' statuses were expired at the close of the reporting period (Table 5). It should be noted that a prescriber is required to enroll every 2 years within the TIRF REMS Access program. Some of these 439 prescribers likely include prescribers who originally enrolled within an individual REMS program and subsequently transitioned to the

TIRF REMS Access program. Enrollment reminders are sent to prescribers at 60-days and 30-days prior to their enrollment expiry date.

Table 5: Prescriber Inactivations

	Current Reporting Period[a] 28APR2012 to 28OCT2012	Cumulative[b] 28DEC2011 to 28OCT2012
Parameter	**N (%)**	**N (%)**
Number of Inactivated Prescribers	445	642
Reason(s) For Inactivation[c]		
Deceased	2 (0.5%)	4 (0.6%)
Program Opt-Out	4 (0.9%)	6 (0.9%)
Expired	439 (98.7%)	632 (98.4%)
Expired at end of period[d]	409 (93.2%)	584 (92.4%)

Note: Percentages are based on the total number (N) for the relevant stakeholder/period.

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

[b] Cumulative is sum of consecutive reporting period totals.

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

[d] Prescribers whose status is 'Inactive - Expired' at the end of the period. Percentages are based on the total number (N) of prescribers with 'Inactivate - Expired' status at least once.

Data Sources: Table 6a: MCK_UBC_TIRF_FDA_Reporting_Enrollment_Status_History_110220121036.txt
MCK_UBC_TIRF_FDA_Reporting_Enrollment_110220121036.txt

Among 1,843 newly enrolled prescribers who attempted and completed the knowledge assessments, 82.2% completed the assessments via the Web and 17.9% completed them via fax (Table 6). Most prescribers passed the knowledge assessments on the first attempt (49.5%) or second attempt (32.6%). Forty-eight (2.6%) prescribers enrolled during this assessment period required more than 4 attempts to successfully complete the knowledge assessments.

Prescribers who take 6 attempts to complete the Knowledge Assessment are "suspended" in the TIRF REMS Access program until a representative from the Call Center can conduct outreach to provide additional educational assistance.

Table 6: Enrolled Prescriber Completed Knowledge Assessments and Number of Attempts to Complete

	Current Reporting Period 28APR2012 to 28OCT2012	Cumulative[a] 28DEC2011 to 28OCT2012
Parameter	**N (%)**	**N (%)**
Number of Enrolled Prescribers Successfully Completing Knowledge Assessment (KA)	1,843	4,296
Method of KA Completion		
Web	1,514 (82.1%)	3,729 (86.8%)
Fax	329 (17.9%)	567 (13.2%)
Number of Prescribers with One or More Attempts to Successfully Complete Knowledge Assessment[b]		
One attempt	912 (49.5%)	1,983 (46.2%)
Two attempts	600 (32.6%)	1,405 (32.7%)
Three attempts	210 (11.4%)	593 (13.8%)
Four attempts	73 (4.0%)	189 (4.4%)
Five attempts	30 (1.6%)	76 (1.8%)
Six attempts	12 (0.7%)	36 (0.8%)
Greater than six attempts	6 (0.3%)	14 (0.3%)

Note: Percentages are based on the total number (N) of prescribers successfully enrolled in the period.

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

[b] Limited to successfully enrolled prescribers completing a Knowledge Assessment.

Data Sources: Table 2a: MCK_UBC_TIRF_FDA_Reporting_KA_110220121036.txt

5.2.3 Pharmacy Enrollment, Inactivation, and Education [Metric 10, 11, 12]

During the current reporting period, there were 2,595 newly enrolled pharmacies from all 50 states, as well as the District of Columbia, Guam, Puerto Rico, and the Virgin Islands. These included independent outpatient pharmacies (45.4%), corporate pharmacy stores (41.7%), inpatient pharmacies (12.6%), and corporate pharmacy headquarters (0.4%) (Table 7).

The states where pharmacies had the highest proportion of enrolled pharmacies included California (10.5%), Florida (8.7%), Texas (8.7%), New York (6.6%), Pennsylvania (4.4%),

North Carolina (4.4%), New Jersey (4.1%), Missouri (3.7%), and Maryland (3.2%); all other states had enrollment ≤2.8%.

As shown in Table 7, the method of enrollment for the majority of pharmacies was via the Web (51.1%), their corporate chain (45.3%; i.e., enrollment occurred via file enrollment upload), or manually by fax (3.6%).

There were 61 incomplete pharmacy enrollment forms received for pharmacies that enrolled via fax. The reasons most often reported for incompleteness were invalid DEA number (4.9%), missing DEA number (3.3%), invalid NPI (1.6%), invalid NCPDP (1.6%), and missing state license number (1.6%). It should be noted that each form may have multiple reasons and could have been submitted multiple times.

As described for prescribers, pharmacies that enroll via Web do not submit forms, but instead move through a series of modules. At any given time in the process, one or more modules may be incomplete. Pharmacies cannot enroll via Web unless all modules/requirements are completed. There were a number of outpatient (N=198), inpatient pharmacies (N=35), and corporate pharmacy headquarter/stores (N=47) who initiated enrollment via the Web but did not complete enrollment as of the last date of the current reporting period (28 October 2012; data on file). The major reasons for incomplete enrollment of outpatient pharmacies were as follows: no attestation (98, 49.5%), pending test transaction verification (97, 49.0%), and training not complete (87, 43.9%). The major reasons for incomplete enrollment of inpatient pharmacies were no attestation (35, 100.0%) and invalid DEA number (8, 22.9%). The major reasons for incomplete enrollment of corporate pharmacy stores were training not complete (47, 100.0%), and invalid DEA number (6, 12.8%).

Table 7: Pharmacy Enrollment

	Current Reporting Period 28APR2012 to 28OCT2012	**Cumulative[a] 28DEC2011 to 28OCT2012**
Parameter	**N (%)**	**N (%)**
Number of Enrolled Pharmacies[b]	2,595 [c]	37,968 [c]
Independent Outpatient	1,177 (45.4%)	4,537 (12.0%)
Corporate Pharmacy Headquarters	10 (0.4%)	89 (0.2%)
Corporate Pharmacy Stores	1,081 (41.7%)	32,622 (85.9%)
Inpatient	327 (12.6%)	720 (1.9%)
Method of Successful Enrollments[d]		
The Web	1,326 (51.1%)	4,882 (12.9%)
Fax	94 (3.6%)	170 (0.5%)
File (file enrollment upload)	1,175 (45.3%)	32,916 (86.7%)

(continued)

Table 7: Pharmacy Enrollment

	Current Reporting Period 28APR2012 to 28OCT2012	Cumulative[a] 28DEC2011 to 28OCT2012
Parameter	**N (%)**	**N (%)**
State/Territory of Pharmacy Primary Address[e]		
Alabama	42 (1.6%)	637 (1.7%)
Alaska	2 (0.1%)	54 (0.1%)
Arizona	26 (1.0%)	815 (2.2%)
Arkansas	33 (1.3%)	249 (0.7%)
California	273 (10.5%)	3,685 (9.7%)
Colorado	50 (1.9%)	601 (1.6%)
Connecticut	26 (1.0%)	483 (1.3%)
Delaware	7 (0.3%)	154 (0.4%)
Florida	225 (8.7%)	3,076 (8.1%)
Georgia	65 (2.5%)	1,391 (3.7%)
Hawaii	22 (0.9%)	117 (0.3%)
Idaho	4 (0.2%)	156 (0.4%)
Illinois	72 (2.8%)	1,494 (3.9%)
Indiana	42 (1.6%)	877 (2.3%)
Iowa	13 (0.5%)	222 (0.6%)
Kansas	13 (0.5%)	272 (0.7%)
Kentucky	25 (1.0%)	496 (1.3%)
Louisiana	60 (2.3%)	523 (1.4%)
Maine	5 (0.2%)	159 (0.4%)
Maryland	83 (3.2%)	820 (2.2%)
Massachusetts	22 (0.9%)	880 (2.3%)
Michigan	64 (2.5%)	1,410 (3.7%)
Minnesota	18 (0.7%)	543 (1.4%)
Mississippi	57 (2.2%)	309 (0.8%)
Missouri	96 (3.7%)	633 (1.7%)
Montana	9 (0.4%)	102 (0.3%)
Nebraska	11 (0.4%)	187 (0.5%)
Nevada	22 (0.9%)	327 (0.9%)
New Hampshire	4 (0.2%)	176 (0.5%)
New Jersey	107 (4.1%)	1,297 (3.4%)
New Mexico	8 (0.3%)	169 (0.5%)
New York	171 (6.6%)	2,269 (6.0%)

(continued)

Table 7: Pharmacy Enrollment

	Current Reporting Period 28APR2012 to 28OCT2012	Cumulative[a] 28DEC2011 to 28OCT2012
Parameter	**N (%)**	**N (%)**
North Carolina	115 (4.4%)	1,254 (3.3%)
North Dakota	5 (0.2%)	48 (0.1%)
Ohio	72 (2.8%)	1,599 (4.2%)
Oklahoma	26 (1.0%)	362 (1.0%)
Oregon	34 (1.3%)	416 (1.1%)
Pennsylvania	113 (4.4%)	1,942 (5.1%)
Rhode Island	4 (0.2%)	161 (0.4%)
South Carolina	44 (1.7%)	674 (1.8%)
South Dakota	7 (0.3%)	52 (0.1%)
Tennessee	53 (2.0%)	885 (2.3%)
Texas	226 (8.7%)	2,541 (6.7%)
Utah	29 (1.1%)	303 (0.8%)
Vermont	1 (<0.1%)	79 (0.2%)
Virginia	64 (2.5%)	1,048 (2.8%)
Washington	40 (1.5%)	785 (2.1%)
West Virginia	14 (0.5%)	298 (0.8%)
Wisconsin	37 (1.4%)	612 (1.6%)
Wyoming	7 (0.3%)	70 (0.2%)
District of Columbia	16 (0.6%)	100 (0.3%)
Guam	0	1 (<0.1%)
Puerto Rico	10 (0.4%)	152 (0.4%)
Virgin Islands	1 (<0.1%)	3 (<0.1%)
Number of Incomplete Pharmacy Enrollment Forms Received for Fax Enrolled Pharmacies[f]	61[g]	131[g]
Missing DEA Number	2 (3.3%)	21 (16.0%)
Invalid DEA Number	3 (4.9%)	16 (12.2%)
Missing NPI Number	0	9 (6.9%)
Invalid NPI Number	1 (1.6%)	7 (5.3%)
Not Agreed to Terms and Conditions	0	7 (5.3%)
Invalid NCPDP Number	1 (1.6%)	6 (4.6%)
Missing NCPDP Number	0	4 (3.1%)
Missing Email	0	3 (2.3%)

(continued)

Table 7: Pharmacy Enrollment

	Current Reporting Period 28APR2012 to 28OCT2012	Cumulative[a] 28DEC2011 to 28OCT2012
Parameter	**N (%)**	**N (%)**
Missing State License Number	1 (1.6%)	3 (2.3%)
Missing Fax Number	0	1 (0.8%)
Missing Pharmacist Phone Number	0	1 (0.8%)

Note: Percentages are based on the total number (N) for stakeholders for the period.

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

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

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

[d] Method Definitions: *Web* – enrollment occurred via program Web site; *Fax* – enrollment occurred via fax sent to the Call Center; *File* – enrollment occurred via custom file load (e.g. chain stores).

[e] Pharmacies are classified by the primary address for the Pharmacist in Charge as recorded on the enrollment form.

[f] Percentage is based on the total number of incomplete forms received in the reporting period. Forms may be incomplete for more than one reason.

[g] Does not include pharmacies that transitioned into the TIRF REMS Access program from other individual REMS programs.

Data Sources: Table 1b: MCK_UBC_TIRF_FDA_Reporting_Pharmacy_110220121036.txt
MCK_UBC_TIRF_FDA_Reporting_Enrollment_Status_History_110220121036.txt
MCK_UBC_TIRF_FDA_Reporting_Enrollment_110220121036.txt

There were 2 (33.3%) inpatient pharmacies and 4 (66.7%) outpatient pharmacies inactivated at least once during this reporting period. The reason for all 6 inactivations was due to the pharmacy opting out of the program.

Table 8: Reasons for Pharmacy Inactivations

	Current Reporting Period[a] 28APR2012 to 28OCT2012	Cumulative[b] 28DEC2011 to 28OCT2012
Parameter	**N (%)**	**N (%)**
Number of Inactivated Pharmacies	6	6
Inpatient	2 (33.3%)	2 (33.3%)
Outpatient	4 (66.7%)	4 (66.7%)
Reason(s) for Inpatient Inactivation[c]		
Program Opt-Out	2 (100.0%)	2 (100.0%)
Reason(s) for Outpatient Inactivation[d]		
Program Opt-Out	4 (100.0%)	4 (100.0%)

[a] Pharmacies with 'inactive' status at least once during the period.
[b] Cumulative is sum of 'reporting period' totals.
[c] Percentages are based on the total number (N) of inactivated inpatient pharmacies. An inpatient pharmacy may have more than one reason for inactivation.
[d] Percentages are based on the total number (N) of inactivated outpatient pharmacies. An outpatient pharmacy may have more than one reason for inactivation.
Data Source**:** MCK_UBC_TIRF_FDA_Reporting_Enrollment_Status_History_110220121036.txt

Of the 2595 newly enrolled pharmacies in this reporting period, a total of 890 authorized pharmacists/pharmacy representatives completed the knowledge assessment (Table 9). The majority of authorized pharmacists/completed the knowledge assessment on the first attempt (43.0%) or the second attempt (37.3%). There were 6.9% authorized pharmacists/that required four or more attempts to successfully complete the knowledge assessment. Authorized pharmacists who take 6 attempts to complete the knowledge assessment are “suspended” in the TIRF REMS Access program until a representative from the Call Center can conduct outreach to provide additional educational assistance.

The number of authorized pharmacists is lower than the number of enrolled pharmacies since pharmacies that were transitioned from an individual REMS program were not required to complete the TIRF REMS Access program knowledge assessment. Also, an authorized pharmacist/pharmacy representative may have been in charge of more than one store. Additionally, the TIRF REMS Access program does not manage the education of the chain pharmacy stores; this is done by the corporate chain headquarters. However, training and education data are available to the TIRF REMS Access program via audit.

Table 9: Enrolled Authorized Pharmacist/Pharmacy Knowledge Assessments and Attempts Needed to Complete

	Current Reporting Period[a] 28APR2012 to 28OCT2012	Cumulative[a,b] 28DEC2011 to 28OCT2012
Parameter	**N (%)**	**N (%)**
Number of Authorized Pharmacists/Pharmacy Representatives Successfully Completing Knowledge Assessment	890[c]	3,173
Number of Authorized Pharmacists with One or More Attempts to Successfully Complete Knowledge Assessment[d]		
One attempt	383 (43.0%)	1,254 (39.5%)
Two attempts	332 (37.3%)	1,210 (38.1%)
Three attempts	114 (12.8%)	476 (15.0%)
Four attempts	36 (4.0%)	151 (4.8%)
Five attempts	14 (1.6%)	53 (1.7%)
Six attempts	7 (0.8%)	21 (0.7%)
Greater than six attempts	4 (0.5%)	8 (0.3%)

Note: Percentages are based on the total number (N) of pharmacists for the period.

[a] Includes pharmacies that transitioned into the TIRF REMS Access program from other individual REMS programs.

[b] Cumulative from the end of prior period may differ from last period's report due to reconciliation of duplicates.

[c] For chain pharmacies, the results only reflect completion by the corporate headquarters and may not include individual retail locations. Corporate pharmacies are required to certify outlets will complete all applicable assessments to participate in the program.

[d] Limited to successfully enrolled pharmacists.

Data Sources: Table 2b: MCK_UBC_TIRF_FDA_Reporting_KA_110220121036.txt
MCK_UBC_TIRF_FDA_Reporting_Enrollment_Status_History_110220121036.txt

5.2.4 Dispensing Activity [Metric 13 and 14]

A total of 54,614 prescriptions were adjudicated for safety by the TIRF REMS Access program in the current reporting period. Of those adjudicated by the TIRF REMS Access program, 96.3% of those prescriptions were subsequently approved for dispensing (meaning authorized for dispensing by insurance or paid for in cash) (Table 10).

Table 10: Authorized Prescriptions Dispensed from Outpatient Pharmacies

	Current Reporting Period[a] 28APR2012 to 28OCT2012	Cumulative[a] 28DEC2011 to 28OCT2012
Parameter	**N (%)**	**N (%)**
Number of Authorized Prescriptions[b]	54,614	68,781
Number of Authorized Prescriptions Dispensed[c]	52,606 (96.3%)	65,977 (95.9%)

Note: Percentages are based on the total number (N) of authorized prescriptions for the period.

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

[b] Prescription successfully adjudicated for safety (i.e., successful REMS edit).

[c] Indicates number of prescriptions that were adjudicated for safety (i.e., successful REMS edit) and authorized for dispensing by insurance or paid for in cash.

Data Source: Table 3a, RHP_UBC_TIRF_FDA_Network_Data_10282012.txt

A total of 11,313 prescription claims were rejected because they failed to meet REMS requirements for prescriber and/or patient and/or pharmacy. A single prescription may have been submitted and rejected multiple times. The majority of rejection reasons were due to prescriber ID not enrolled or prescriber ID enterers was not found in TIRF REMS Access database (44.8%), PPAF incomplete (22.2%), patient zip code missing from claim (17.3%), prescriber last name did not match name registered (15.2%), or pharmacy was not enrolled (8.3%).

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

Patients with prescriptions from multiple prescribers within an overlapping time frame were assessed, and 505 patients had 3 or more prescribers in a rolling 6-month period (data not shown, which represents approximately 4% of all enrolled patients (N=12,071); Data Source: Table 3b. RHP_UBC_TIRF_FDA_Network_Data_10282012.txt). Patients may have multiple prescribers for various reasons such as patient relocation, prescriber relocation/retirement/death, or patient is seen at a single practice with multiple prescribers. Attempts are made to research reports of patients with prescriptions from 3 or more prescribers in a rolling 6-month period. Outcomes from this research will be included in subsequent reports.

Table 11: Total Number of Prescriptions Rejected for Safety

	Current Reporting Period[a] 28APR2012 to 28OCT2012	Cumulative[a] 28DEC2011 to 28OCT2012
Parameter	**N (%)**	**N (%)**
Number of Prescription Claims Rejected for Safety	11,313	23,121
Reasons For Rejection[b]		
Pharmacy not enrolled	934 (8.3%)	3,053 (13.2%)
Pharmacy enrollment incomplete or expired	87 (0.8%)	431 (1.9%)
System unavailable due to maintenance	3 (<0.1%)	8 (<0.1%)
Prescriber ID not submitted on claim	129 (1.1%)	233 (1.0%)
Prescriber ID not in TIRF REMS Access database	5,065 (44.8%)	10,594 (45.8%)
Prescriber last name did not match name registered	1,714 (15.2%)	2,889 (12.5%)
Prescriber enrollment incomplete or expired	135 (1.2%)	348 (1.5%)
Prescriber enrollment incomplete or expired and prescriber last name mismatch	5 (<0.1%)	27 (0.1%)
DOB missing from claim	18 (0.2%)	27 (0.1%)
Patient first name missing from claim	104 (0.9%)	175 (0.8%)
Patient last name missing from claim	27 (0.2%)	53 (0.2%)
Patient zip code missing from claim	1,952 (17.3%)	3,664 (15.8%)
Multiple patients found	12 (0.1%)	13 (0.1%)
Prescriber decision to deactivate patient	0	0
Patient inactive >= 6mos and must resubmit PPAF	0	0
Patient deceased	0	0
Database failure	0	0
PPAF Incomplete	2,513 (22.2%)	5,303 (22.9%)
PPAF Terminated	28 (0.2%)	42 (0.2%)

Note: Percentages are based on the total number (N) of rejected prescriptions for the relevant period. *Rejected for Safety* is defined in this table to mean the prescription did not pass REMS edits

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

[b] A prescription may be rejected for more than one reason.

Data Source: Table 3c: RHP_UBC_TIRF_FDA_Network_Data_10282012.txt

5.2.5 Wholesaler/Distributor Enrollment [Metric 15 and 16]

During the current reporting period, no wholesalers/distributors were newly enrolled in the REMS program (Table 12).

No wholesalers/distributors were inactivated (data not shown in Table 11; Data Sources Table 6d: MCK_UBC_TIRF_FDA_Reporting_Enrollment_Status_ History_110220121036.txt

Table 12: Wholesaler/Distributor Enrollment

	Current Reporting Period[a] 28APR2012 to 28OCT2012	Cumulative[a,b] 28DEC2011 to 28OCT2012
Parameter	**N (%)**	**N (%)**
Number of Wholesalers/Distributors Enrolled	0	40
Method of Enrollment		
Fax	0	18 (45.0%)
File	0	22 (55.0%)
Number of Incomplete Wholesaler/ Distributor Enrollment Forms Received	0	0

Note: Percentages are based on the total number (N) for the relevant Wholesalers/Distributors for the period.

[a] Includes Wholesalers/Distributors that transitioned into the TIRF REMS Access program from other individual REMS programs.

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

Data Source: Table 1d: MCK_UBC_TIRF_FDA_Reporting_Enrollment_Status_History_110220121036.txt

5.2.6 Barriers or Delays in Patient Access [Metric 17 and 18]

A total of 4,437 PPAFs were submitted to the REMS program either via the Web (75.5%) or by fax (24.5%). At least 36.4% of PPAFs were received the same day or within 10 days (25.6% on the same day and 10.8% between 1 and 10 days) (Table 13 and Figure 1).

Table 13: Submission of Patient-Prescriber Agreements to the REMS Program

	Current Reporting Period 28APR2012 to 28OCT2012	Cumulative[a, b] 28DEC2011 to 28OCT2012
Parameter	**N (%)**	**N (%)**
Number of Patient-Prescriber Agreement Forms Submitted to REMS Program	4,437	10,127
Method of PPAF Submission		
The Web	3,349 (75.5%)	7,313 (72.2%)
Fax	1,088 (24.5%)	2,205 (21.8%)
One-time file upload	0	609 (6.0%)
Number of Forms Received by Days Elapsed between Patient Enrollment and Receipt of Patient-Prescriber Agreement by REMS Program		
Form Received Same Day	1,134 (25.6%)	3,066 (30.3%)
Form Received between 1 and 10 days	478 (10.8%)	1,294 (12.8%)
Form Received between 11 and 15 days	241 (5.4%)	511 (5.1%)
Form Received between 16 and 20 days	164 (3.7%)	464 (4.6%)
Form Received between 21 and 30 days	872 (19.7%)	2,524 (24.9%)
Form Received >30 days after Patient Enrollment	1,548 (34.9%)	2,268 (22.4%)

Note: Percentages are based on the total number (N) of forms for the period.

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

[b] Cumulative total from the end of prior reporting period may differ from current period's report due to reconciliation of patients with completed enrollment.

Data Sources: Table 4a: MCK_UBC_TIRF_FDA_Reporting_PPAF_110220121036.txt
MCK_UBC_TIRF_FDA_Reporting_Enrollment_110220121036.txt

Figure 1: PPAF Receipt by Time Since Patient Enrollment (28APR2012 to 28OCT2012)

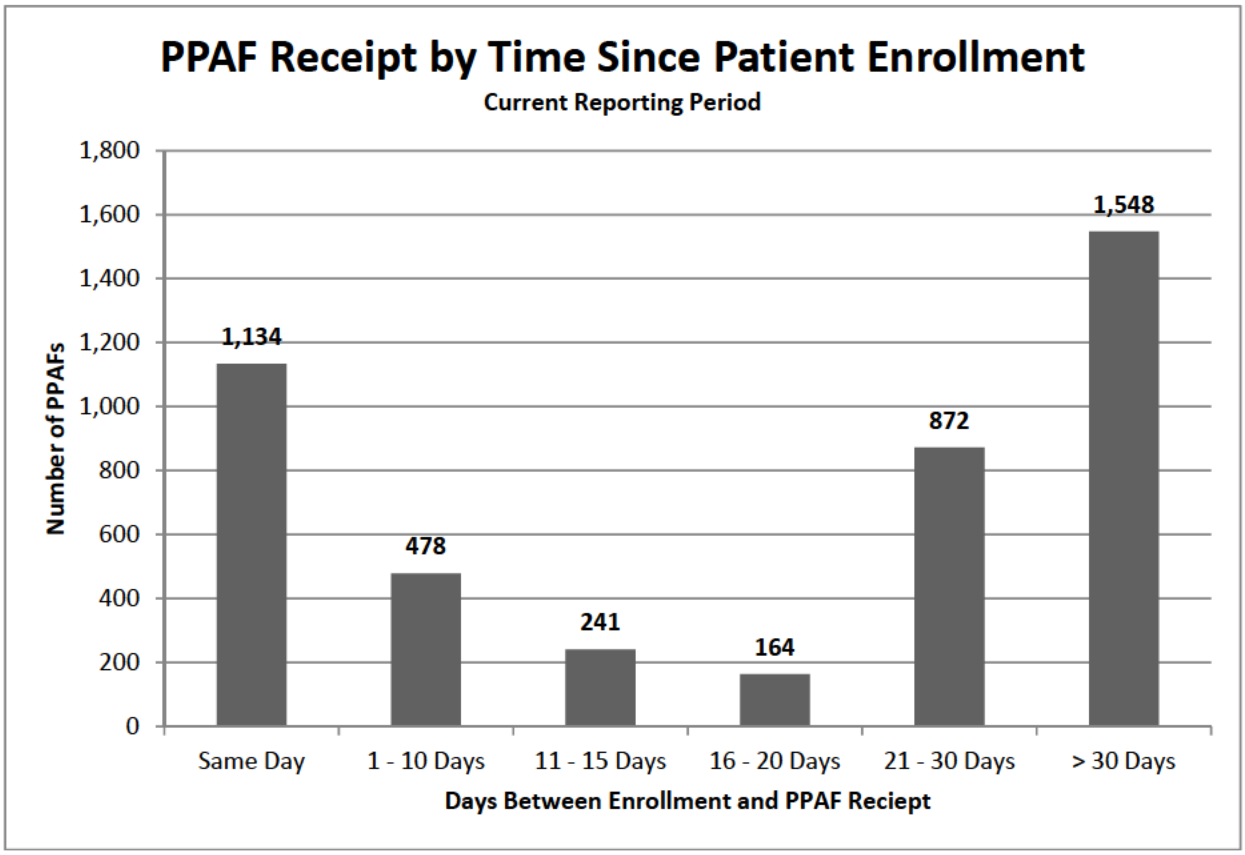

Figure Source: Table 4a: MCK_UBC_TIRF_FDA_Reporting_PPAF_110220121036.txt
MCK_UBC_TIRF_FDA_Reporting_Enrollment_110220121036.txt

A total of 7,444 prescriptions were dispensed to a total of 4,244 patients during the first 10 days after patient enrollment (Table 14 and Figure 2 below). There were a greater number of patients who had their first prescription filled in the first 10 days without a PPAF compared with those patients with a PPAF (71.4% vs. 14.2%). For patients without a PPAF, the majority of patients (80%) received only 1 fill.

It was observed that 1 patient received more than 3 fills in a 10-day period without a PPAF on file. This report will be investigated and the outcome of this research will be reported in next assessment report. Additionally, the TIRF REMS Access program is exploring the root cause for these events to identify possible system enhancements.

Table 14: Prescriptions Dispensed During the First 10 Days after Patient Enrollment

	Current Reporting Period 28APR2012 to 28OCT2012	Cumulative[a] 28DEC2011 to 28OCT2012
Parameter	**N (%)**	**N (%)**
Number of prescriptions dispensed to patients during the first 10 days after patient enrollment	4,960	12,796
Number of patients dispensed a prescription during the first 10 days after patient enrollment	4,442	11,000
With PPAF[b]		
1 Fill	760 (17.1%)	1,417 (12.9%)
2 Fills	78 (1.8%)	222 (2.0%)
3 Fills	13 (0.3%)	34 (0.3%)
>3 Fills	2 (<0.1%)	12 (0.1%)
Without a PPAF[b, c]		
1 Fill	3,566 (80.3%)	8,978 (81.6%)
2 Fills	184 (4.1%)	704 (6.4%)
3 Fills	19 (0.4%)	112 (1.0%)
>3 Fills	1 (<0.1%)	10 (0.1%)

[a] Cumulative data from the end of the 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.

Data Source: Table 4b: RHP_UBC_TIRF_FDA_Network_Data_10282012.txt

Figure 2: Number of Patients Dispensed a Prescription During the First 10 Days After Patient Enrollment (28APR2012 to 28OCT2012).

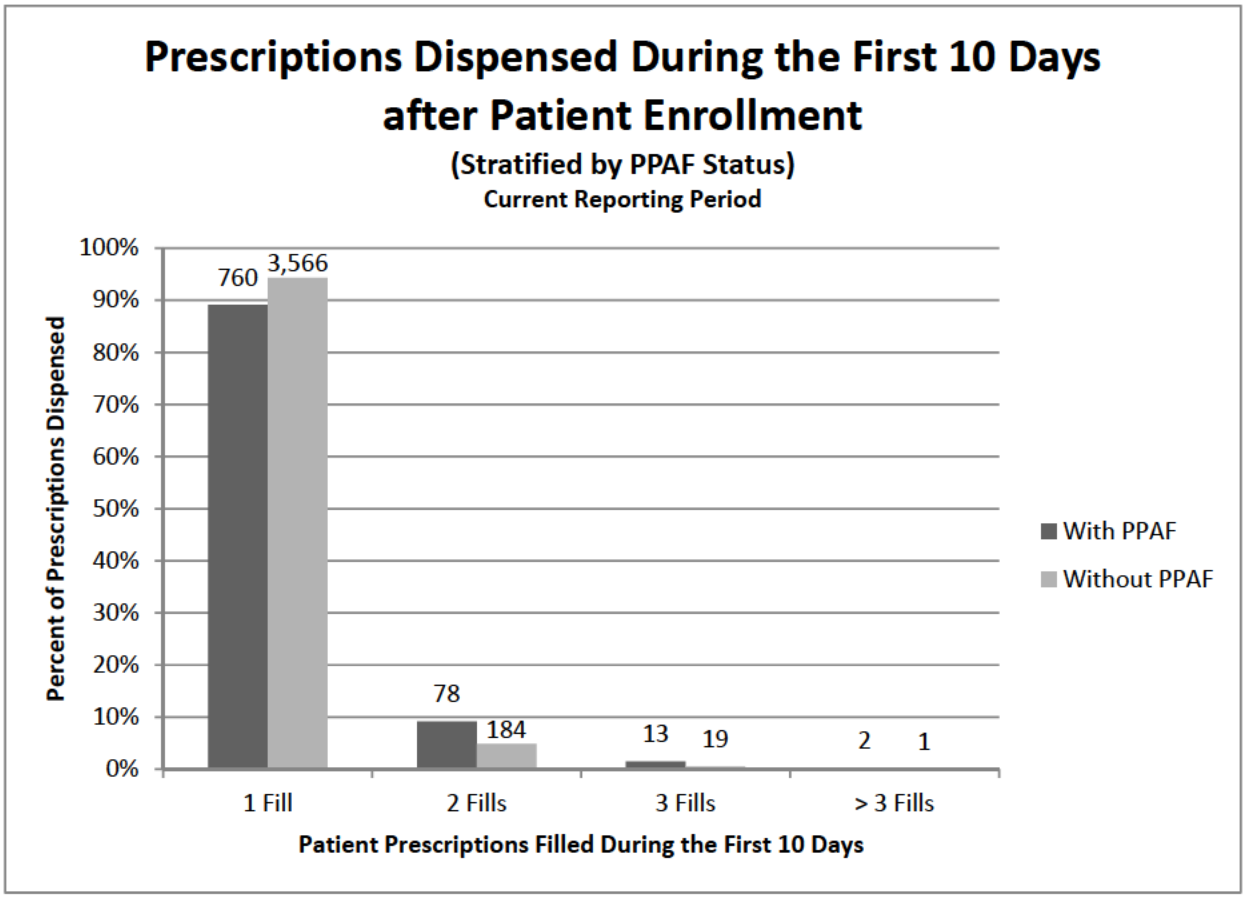

Figure Source: Table 4b: RHP_UBC_TIRF_FDA_Network_Data_10282012.txt

It was previously reported to FDA that 29 patients received more than 3 fills without a PPAF on file in a 10-day period. Upon additional research, 13 of the 29 patients did have a PPAF on file prior to receiving the 4th prescription. These 13 patients were incorrectly reported as not having a PPAF on file in the previous assessment report. The remaining 16 patient transactions were reviewed in detail and the outcomes of this research are reported below:

- Pharmacy data entry errors: Ten (10) of the 16 patients were identified as receiving more than 3 prescriptions within a 10-day grace period due to data entry errors made by 16 pharmacies. When patient prescriptions are processed by the TIRF REMS, the patient is passively enrolled in the program. In order for passive enrollment to occur, a communication is completed with the REMS Administrator to obtain a unique patient identifier. In this scenario, patient prescriptions are submitted for the same patient with slightly different information. When the prescription was sent to the REMS

Administrator, the patient was issued a new patient identifier (although they had already been previously enrolled). The system was unable to identify that this patient was the same patient because it relies on exact data. These 16 pharmacies were able to receive approval from the TIRF REMS system because the patient data were different between the claims to appear as if the transaction was for a new patient. All of these reports will be further investigated to identify any issues of non-compliance and updates will be provided in the next report.

As of 11 December 2012, 8 of the 10 patients now have a PPAF on file. As mentioned above, the TIRF REMS Access program is exploring system and program enhancements to mitigate the possibility for these events in the future.

- Duplicate patient records: Six (6) of the 16 patients were identified as receiving more than 3 prescriptions within the 10 day grace period due to the pharmacy process that was used to transmit the paid claims. The pharmacy submitted multiple prescriptions sub-seconds apart, which did not allow the TIRF REMS the ability to process the enrollment for the patient. When multiple prescriptions are submitted simultaneously, TIRF REMS will create two patient records that are not immediately identified as being the same patient. These instances are automatically investigated in real-time and resolved as duplicate records. As of 11 December 2012, all 6 patients now have a PPAF on file.

TIRF REMS currently performs outreach to prescribers to obtain a PPAF. TIRF REMS has performed additional outreach to the prescribers to obtain a PPAF for the remaining 2 patients.

5.3 Program Infrastructure and Performance [Metrics 19, 20, 21, 22, 23, 24]

5.3.1 Pharmacy Management Systems [Metric 19]

Table 15 summarizes the time it took enrolled outpatient pharmacies to configure their PMS to communicate with the REMS program. Of 682 outpatient pharmacies that attempted to configure a PMS, 96.5% successfully reconfigured their systems and 3.5% did not complete configuration of their PMS within the reporting period. It took a mean of 2.49 days to configure, with a minimum of 0.0002 days and a maximum of approximately 189.97 days.

Table 15: Configuration of Pharmacy Management System (PMS)

	Current Reporting Period 28APR2012 to 28OCT2012	Cumulative 28DEC2011 to 28OCT2012
Parameter	**N (%)**	**N (%)**
Number of Outpatient Pharmacies Attempting to Configure PMS	682	2,816
Number of Pharmacies with Incomplete Configuration of PMS[a]	24 (3.5%)	51 (1.8%)
Number of Outpatient Pharmacies Successfully Completing Configuration of PMS[b]	658 (96.5%)	2,765 (98.2%)
Time Required to Complete Configuration[c]		
Mean	2.4920	0.8239
Minimum	0.0002	0.0001
Maximum	189.97	189.97

[a] Defined as number of pharmacies with less than 3 dates of test transfers in the reporting period.

[b] Percentages are based on the total number (N) of pharmacies attempting to configure their PMS for the relevant period. For chain pharmacies, this refers to their corporate office(s), not individual locations.

[c] Time measured in days from 1st transaction attempt to final transaction success.

Data Source: Table 5: RHP_UBC_TIRF_FDA_Network_Data_10282012.txt

In the previous reporting period, (28 December 2011 to 27 April 2012), it was reported that 81 pharmacies did not complete configuration of their PMS.

Of these 81 pharmacies, 8 pharmacies were considered chain pharmacies and inadvertently enrolled as independent pharmacies. These 8 chain pharmacies are now currently enrolled in the TIRF REMS Access program. Of the 73 independent pharmacies pending system configuration:

- 19 have successfully completed their pharmacy system configuration
- 35 were identified as independent pharmacies transitioned to the TIRF REMS Access program from a previous independent REMS program for a TIRF medicine who inadvertently began the pharmacy system configuration process again
    - This step was not a requirement for enrollment as it was completed at the time of enrollment in the independent program. The only requirement necessary for these transitioned pharmacies to become enrolled in the TIRF REMS Access program was to acknowledge the updated terms and conditions for the program.

- This step was completed and confirmed for these 35 independent pharmacies and they are actively enrolled in the program
- 10 have chosen to "opt out" of the program
- 9 have not configured their system as of the end of the reporting period.

5.3.2 Backup System for Prescription Validation [Metric 20]

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.

5.3.3 REMS Call Center [Metric 21a, b]

Table 16 below shows reasons for contacting the REMS Call Center by frequency (%). For presentation in the report, the table cut-off is at least 80% of the total cumulative frequency of contact reasons. The most frequent reasons classified under the call reason were pharmacy:pharmacy claim rejection (15.11%), enrollment status inquiry (14.06%), prescriber:pharmacy claim rejection (11.73%), and PPAF follow up or status inquiry (20.92%). The call reasons listed below in Table 16 represent 81.01% of calls to the Call Center for the current reporting period.

Table 16: Reasons and Frequency for Contacting the Call Center

Contact Reason	Current Reporting Period 28APR2012 to 28OCT2012		
	Frequency	Percent[a]	Cumulative Percent
Pharmacy: Pharmacy Claim Rejection	2594	15.11	15.11
Enrollment Status Inquiry	2414	14.06	29.17
Prescriber: Pharmacy Claim Rejection	1952	11.73	40.54
PPAF Status Inquiry or Follow-up	3592	20.92	61.46
Patient: Pharmacy Claim Rejection	1246	7.26	68.72
General Program Questions	1056	6.15	74.87
Enrollment Follow Up	1053	6.13	81.01

[a] The total percentage presented in the table is 81.01% of all reasons for contacting the Call Center.Source: Data on file (The FREQ Procedure).

Problems or complaints that were reported to the REMS Call Center for review by the TIRF REMS Access program are summarized below. Additional Call Center issues that met the definition of non-compliance are presented in Section 6, Report #12.

ID #1: Open [Patient Access]
Issue: On 23 August 2012, a complaint letter was received from a prescriber regarding attestation language in the PPAF. The prescriber complained that the TIRF REMS requirement regarding opioid tolerance does not allow the physician to provide "best possible pain management to patients" and possibly requires "over-prescribing of pain medication."

Resolution: A copy of the letter was submitted to FDA. This prescriber is currently enrolled in the TIRF REMS Access program and has prescribed TIRF medicines. There was one paid claim recorded in the TIRF REMS Access program for this prescriber.

ID #2: Closed [Patient Access]
Issue: On 10 September 2012, a pharmacy and a prescriber attempted to enroll with a shared DEA. The prescriber is a physician and also the owner of outpatient pharmacy. The pharmacy was successfully enrolled in April 2012. The prescriber attempted to enroll in September 2012 using the same DEA number as used by the pharmacy; however, the REMS application did not allow the prescriber to enroll because the DEA number was already in use.

Resolution: An outreach was conducted to the DEA office that governs the prescriber's area (New York). The DEA office confirmed the legitimacy of the prescriber and approved the outpatient pharmacy and prescriber to enroll in the TIRF REMS and share the same DEA number so long as both records were enrolled with the same address. The prescriber was successfully enrolled on 26 October 2012.

ID #3: Open [Patient Access]
Issue: On 03 October 2012, a prescriber submitted a written complaint over PPAF attestation language. The TIRF REMS received a modified PPAF from the prescriber because the patient is not on around-the-clock opioid medication. The call center advised the prescriber that an altered PPAF could not be processed and requested the prescriber resubmit the PPAF. The same PPAF was re-submitted with letter of explanation from the patient's physician describing the patient's condition (i.e., not on ATC opioids). The PPAF was not processed because it was an altered PPAF and therefore did not meet the TIRF REMS requirements.

Resolution: An email was sent to FDA requesting a teleconference.

ID #4: Closed

Issue: Seven (7) escalations have been reported for cases identified within this reporting period where a TIRF REMS Access program call center agent conducted outreach to prescribers' offices to obtain a PPAF for an enrolled patient, and the offices all confirmed the patient was not a patient of the prescribers' office. The issue was identified as a result of pharmacies selecting the incorrect patient profiles within their pharmacy management systems. Upon

investigation, the pharmacies all confirmed that they immediately reversed the claim and re-submitted the claim by selecting the correct patient profile. As a result of the incorrect patient being submitted on the initial transaction, the patient enrollment record was created in the TIRF REMS Access database but later removed when the pharmacy error was confirmed.

Resolution: The patient enrollment records that were created as result of this error have been removed from the TIRF REMS database.

5.4 System Errors and Corrective Actions [Metric 22]

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 #1
Description: Part of the TIRF REMS networking software, a Passive Patient Queue, was not submitting some updates to the TIRF REMS Access program for passive patient enrollment between 16 May 2012 and 23 May2012. This resulted in 136 unique patients not being passively enrolled in TIRF REMS. The passive patient enrollment is designed to determine if there are more than 3 prescriptions received in a 10-day grace period because a Prescriber Patient Agreement Form is required if this count is exceeded. A total of 168 transactions were impacted by the queuing issue with 136 unique patients not passively enrolled. However, there were no patients that received more than 3 scripts in a 10-day grace period and all effected patients have been passively enrolled in TIRF REMS.

Root Cause: Part of the TIRF REMS networking software, a Passive Patient Queue, was not submitting some updates to the TIRF REMS.

Correction: The connection to the Passive Patient Queue was updated on 24 May2012 and 136 new patient records were sent to TIRF REMS for passive enrollment. TIRF REMS patient IDs were updated in TIRF REMS History database as well as updated in all reporting tools designed for TIRF REMS. The failed patient queue is now monitored daily and an email alert is sent to the support team when web service calls are not delivered or have failed.

System Error #2
Description: On 04 June 2012, one switch provider, (b) (4) experienced a spontaneous server incident where one TIRF REMS claim bypassed the TIRF REMS validation process. During the period of interruption, the prescription was dispensed without being validated or authorized by the TIRF REMS Access program and was sent directly to the payer for payment. It was verified that only one transaction was not validated by TIRF REMS at time of dispense. The pharmacy and the prescriber were enrolled at the time the prescription was transmitted.

Root Cause: Switch provider server interruption.

Correction: On 02 October 2012, the switch provider informed TIRF REMS that a server fix was implemented for future spontaneous interruptions. (b) (4) updated their servers from 24 September 2012 and 28 September 2012.

System Error #3

Description: On 28 June 2012, (b) (4) pharmacy chain attempted to enroll in TIRF REMS under the chain enrollment umbrella. When the chain attempted to complete the enrollment, they transmitted the incorrect chain ID in their vendor certification transactions, which resulted in an enrollment error. When the transactions were submitted incorrectly, a web service call failure was generated which triggered an email alert to the TIRF REMS Access program. As per current standards, TIRF REMS should have performed an outreach to (b) (4) to correct the issue with their enrollment. Upon investigation, it was determined on 30 August 2012 that the issue with the pharmacy chain completing the enrollment was still open and TIRF REMS Access program had not contacted the chain to correct the enrollment error.

Root Cause: TIRF REMS Access program did not follow-up on a failed enrollment message .

Correction: (b) (4) successfully enrolled on 30 August 2012. Standard Operating Procedures (SOP) were written to clarify actions needed when a REMS web service failure occurs. Training on the SOP for TIRF REMS team was completed on 18 September 2012.

System Error #4

Description: (b) (4) stores initiated inbound calls to the TIRF REMS call center because they were receiving rejections of "M/I Prescriber Last Name." (b) (4) sent the claims back to TIRF REMS for validation, but should have sent them directly to a payer or re-submitted them to the TRIF REMS without removing the prescriber's last name, per (b) (4) specifications. TIRF REMS transactions were correctly validated. There were a total of 1,457 transactions rerouted to TIRF REMS that received the rejection of "M/I Prescriber Last Name," of which 617 were unique prescriptions. This resulted in the rejection of these transactions, and (b) (4) pharmacies were unable to dispense the TIRF REMS medication at the time the rejection was received.

Root Cause: (b) (4) discovered that they made switch channel updates between 29 August 2012 and 07 September 2012, which resulted in TIRF REMS transactions being rerouted for a second validation check. (b) (4) should not route any transactions to TIRF REMS that were sent to them by TIRF REMS.

Correction: On 12 September 2012, (b) (4) was notified by TIRF REMS of the issue and (b) (4) begin to research the routing problem on their end. (b) (4) immediately added

additional logic to the TIRF REMS set up so that claims originating from TIRF REMS would be routed to the payer for payment. On 13 September 2012, the TIRF REMS identified that the issue is resolved and the TIRF REMS call center contacted all (b) (4) stores that reported the problem to ensure that all stores were able to process. On 18 September 2012, (b) (4) advised the TIRF REMS program of internal organizational updates to mitigate this risk going forward.

System Error #5

Description: On 19 October 2012, TIRF REMS had a hardware problem (conversion network adapter overheat) that resulted in TIRF REMS transactions to reject due to the TIRF REMS engine not being able to perform a validation check on stakeholder records. The rejection that was sent to the pharmacies was "System Unavailable. Please Try Again Later." There were 461 transactions impacted, of which there was 111 unique prescriptions.

Root Cause: TIRF REMS Access Program had a conversion network adapter overheat that resulted in TIRF REMS transactions to reject due to the TIRF REMS engine not being able to perform a validation check on stakeholder records.

Correction: TIRF REMS Access program identified the issue on 19 October 2012 and fixed the hardware and any data-related issues. Upon investigation, all 111 unique prescriptions were re-processed correctly.

System Error #6

Description: On 07 May 2012, during an override validation confirmation process, it was discovered that the TIRF REMS Access program inadvertently validated 7 identifiers in error by overriding the identifiers submitted on 6 stakeholders' enrollment submissions. Three (3) of the prescribers were enrolled once the identifiers were incorrectly validated. Three (3) prescribers never completed the enrollment process after the identifiers were validated.

Root cause: The TIRF REMS Access program was validating invalid identifiers without benefit of a Work Instruction.

Correction: A Work Instruction was completed, approved, and trained on 24 April 2012. It was determined that the 3 prescribers were inadvertently enrolled for approximately 90-days. Two files were corrected on 28 June 28 2012 and the third file corrected on 29 June 2012. The TIRF REMS Access program identified there was one (1) paid claim by one of the inadvertently enrolled stakeholders. The TIRF REMS Access program contacted all three inadvertently enrolled prescribers and advised them that their enrollment status was changed to incomplete because the program could not validate their DEA number with Schedule II eligibility. One of the 6 prescribers enrolled on 09 July 2012 and all identifiers are confirmed as valid.

System Error #7
Description: Five prescribers were inadvertently enrolled in the TIRF REMS Access program as a result of the prescribers enrolling in the program with facility DEA numbers. The 5 prescribers were notified of the error, and their status was changed to an incomplete status to allow the impacted prescribers to enroll with an eligible individual DEA number.

Root Cause: Prescribers were enrolling in the program with facility DEA numbers.

Correction: It was confirmed that there were no dispensed TIRF prescriptions as a result of the 5 inadvertent prescriber enrollments.

5.4.1 Lack of Enrolled Prescribers and/or Pharmacies for Patients [Metric 23]

During the current reporting period, no reports of lack of enrolled pharmacies were received.

5.4.2 Delays after Prescription Denial [Metric 24]

The prescription conversion time or length of time delay is defined as the length of time between the initial reject on a claim to when it successfully passes all the REMS business rules/edits and is sent to the payer of adjudication.

For the assessment period, 28 April 2012 through 28 October 2012:

- The mean prescription conversion time is 0 days, 11.410 hours.
- The median prescription conversion time is 0 days, 0.194 hours.
- The minimum prescription conversion is 0 days, 0.001 hours.
- The maximum prescription conversion time is 173 days, 3.001 hours.

There was one outlier that impacted the maximum prescription conversion time of 173 days and 3.001 hours. On 12 April 2012, one independent outpatient pharmacy transmitted a TIRF REMS prescription that did not pass the REMS edits. This transaction rejected for invalid date of birth. On 02 October 2012 (173 days later), the pharmacy resubmitted the prescription, the transaction passed the REMS edits, and was paid.

5.5 Unintended System Interruptions [Metrics 25, 26, 27, 28]

5.5.1 Inadvertent Enrollment Deactivations [Metric 25]

Enrollment Deactivation #1: During this reporting period there were a total of 3 inadvertent prescriber deactivations encompassing one incident. This was as a result of incorrect enrollment effective dates assigned to transitioned prescribers. Upon identification of the deactivations, the 3 prescribers records were reverted back to an enrolled status, and all prescribers were notified

of current status. There were no claims impacted during the time the prescribers were inadvertently deactivated.

5.5.2 Reports of False Positives [Metric 26]

During this reporting period, there were no reports of a false positive incident.

5.5.3 Failure of Re-enrollment Notifications [Metric 27]

Re-enrollment notifications were sent to a total of 396 prescribers this reporting period. Of these, 374 prescribers successfully received a notification for re-enrollment via fax. Two prescribers were successfully notified of re-enrollment via email. By the end of the reporting period, there were a total of 22 unique prescribers who have not yet had a successful re-enrollment notification received via fax in spite of multiple attempts.

5.5.4 Reports of False Negatives [Metric 28]

During the reporting period, there were no reports of a false negative transaction.

5.6 Audits

No audits were conducted during the current reporting period and no reasons were identified to conduct a for-cause audit.

6 TIRF REMS Access Program Non-Compliance

During the current reporting period, instances of potential stakeholder non-compliance with the TIRF REMS Access program were reviewed and investigated. The following tables list resolved and pending potential reports of non-compliance, respectively.

Table 17: Pending/Open Reports from Prior Reporting Period: 28 December 2011 to 27 April 2012

Report No.	Report Description	Report Status	Outcome/Resolution
10	Received pharmacist complaint regarding lack of weekend coverage at TIRF REMS Access program Call Center. Pharmacist reported that the prescriber for a prescription was unaware of PPAF requirement and that the patient was in pain. Pharmacist was unable to resolve rejected claim provided the patient with 3 tablets to carry the patient through the weekend. Live Call Center coverage is available Monday through Friday 8am-8pm EST. (The Call Center was not open seven days a week for individual REMS programs.)	Closed	This case was forwarded as an adverse event to the appropriate Sponsor for further research and follow up. Additional investigation is ongoing to confirm the "3 tablets dispensed" were a TIRF medicine. Update: This case was forwarded to the Manufacturer's Product Safety group however no further investigation was completed as it was not deemed to be a potential safety issue.

Table 18 Reports in the Current Reporting Period: 28 April 2012 to 28 October 2012

Report No.[1]	Report Description	Report Status	Outcome/Resolution
12	Call Center: On 30 May 2012, a pharmacy dispensed a TIRF medicine without successfully processing the claim through REMS edits. A pharmacy received a claim reject reason of "prescriber not enrolled" and contacted the call center. A follow-up call was placed to the prescriber to notify of the enrollment requirement before patient could receive the prescription. The pharmacy advised that the insurance would pay for the prescription so the pharmacy processed the transaction as cash and the medication was dispensed without processing through the REMS edits.	Open	Resolution: . The Non-Compliance Team investigated this report and was able to confirm that the patient received a TIRF medicine on 30 May 2012, but there is no evidence of additional attempts to reprocess a claim. The prescriber in question is not enrolled as of the close of this reporting period. The TIRF REMS Access program has made multiple attempts to contact the prescriber. In addition, as of the close of the reporting period the patient still does not have a passive enrollment in TIRF REMS; thus, it appears the patient has not sought out another prescriber. A Non-compliance Notice Letter was sent to the pharmacist in charge at the pharmacy involved.
13	Closed System Pharmacy: The TIRF REMS Access program administrator identified that the program had not received any prescription authorizations since the Closed System Pharmacy effective day of 01 July2012. Following multiple outreach attempts to the Veteran's Administration (VA), the program received contact from the VA Authorized Representative on November 15th confirming that there had been TIRF prescriptions dispensed without obtaining an authorization to dispense from the Closed System Program. (CAPA 341)	Open	The VA conducted a thorough search across the entire VA system and confirmed that there were TIRF prescriptions dispensed between July 1st and the current date that impacted 15 closed system outpatient VA pharmacies. The VA was only able to provide the number of locations and unable to provide the number of dispenses/prescriptions, only the number of locations. The VA confirmed that they have re-educated these 15 locations and ensured that the processes are being followed for receipt of authorization numbers prior to dispensing prescriptions. The re-education will occur across all locations, but they started specifically with the 15 identified above since they have active patients in these locations. The VA is actively working on obtaining all of the data elements the TIRF REMS Access program requested for each of the dispenses that occurred and they stated this unfortunately takes time and a number of rounds of clearance before they are authorized to send it. They anticipate it will be available by the end of November. The VA confirmed that they are working on this as a priority request. The full outcome of this investigation will be reported in the next REMS Assessment Report.

[1] For tracking purposes across TIRF REMS Access program assessment reports, noncompliance reports are numbered consecutively and continuously from the first TIRF REMS Access program assessment report.
Source: Data on file.

7 SAFETY SURVEILLANCE

7.1 Adverse Events

The following summary was produced from the 2012 Q2 release of the FDA's Freedom of Information Act (FOIA) Adverse Event Reporting System (AERS) database which was made publicly available by the FDA in early October, 2012 (See Appendix 11.3 for full report).

The AERS database comprises 3,778,243 cumulative case reports, including 181,428 new reports in the 2012 Q2 quarterly release. Of these case reports, 46 reference a TIRF product covered by the FDA REMS for TIRF medicines, with an event date on or after 28 December 2011. Thirty-six (36) of these case reports specify United States as the Country of Origin, and 26 of these US cases also include one of the individual MedDRA Preferred Terms (PT) of Interest for the TIRF REMS described in the TRIG AERS Safety Surveillance Plan. These MedDRA Preferred Terms of Interest are grouped into the following broad Categories of Interest (TRIG Categories) for aggregate reporting:

- Death
- Overdose (fatal and non-fatal)
- Misuse, abuse, addiction, and diversion
- Inappropriate
- Medication errors
- Accidental

In addition, 1 report includes at least one Preferred Term from the MedDRA Standardized MedDRA Query (SMQ: Broad) *Acute Central Respiratory Depression*, which is included in the AERS analysis as a possible symptom related to the TRIG Categories above. None of the individual Preferred Terms from this SMQ is a TRIG Preferred Term of interest; instead counts of reports listing any PT from this SMQ will be summarized into an aggregate count for the entire SMQ and reported separately.

The following table summarizes the reported adverse event Terms and Categories of Interest that were reported on the case reports for TIRF products that met the selection criteria for this analysis. A total of 36 PTs of Interest for this study were reported across 26 case reports selected for TIRF products that contained a PT of Interest. The most commonly reported Term is "Off label use" (n=18) followed by "Drug prescribing error" (n=7). One (1) additional case report contained a Preferred Term from the MedDRA SMQ Acute central respiratory depression. These counts of the reported PTs and categories are summarized in the table below:

Table 19: Count of Reported Events of Interest Grouped by TRIG Category: Second Quarter 2012

Events by Category	Q2 2012		Total to Date	
	N	%	N	%
Overdose	**0**	0.0%	**0**	0.0%
Accidental overdose	0	0.0%		
Intentional overdose	0	0.0%		
Multiple drug overdose	0	0.0%		
Multiple drug overdose accidental	0	0.0%		
Multiple drug overdose intentional	0	0.0%		
Overdose	0	0.0%		
Death	**0**	0.0%	**0**	0.0%
Accidental death	0	0.0%		
Agonal death struggle	0	0.0%		
Apparent death	0	0.0%		
Brain death	0	0.0%		
Cardiac arrest	0	0.0%		
Cardiac death	0	0.0%		
Cardio-respiratory arrest	0	0.0%		
Death	0	0.0%		
Death neonatal	0	0.0%		
Death of companion	0	0.0%		
Death of relative	0	0.0%		
Respiratory arrest	0	0.0%		
Sudden cardiac death	0	0.0%		
Sudden death	0	0.0%		
Sudden unexplained death in epilepsy	0	0.0%		
Misuse	0	0.0%	**0**	0.0%
Intentional Drug Misuse	0	0.0%		
Medication overuse headache	0	0.0%		
Drug abuse dependence and withdrawal SMQ	*6*	*N/A*		
Abuse	0	0.0%	**0**	0.0%
Drug abuse	0	0.0%		
Drug abuser	0	0.0%		
Ex-drug abuser	0	0.0%		

(continued)

Table 19: Count of Reported Events of Interest Grouped by TRIG Category: Second Quarter 2012

Events by Category	Q2 2012		Total to Date	
	N	%	N	%
Substance abuse	0	0.0%		
Substance abuser	0	0.0%		
Substance-induced mood disorder	0	0.0%		
Substance-induced psychotic disorder	0	0.0%		
Drug abuse dependence and withdrawal SMQ	*6*	*N/A*		
Inappropriate	18	50.0%	18	50.0%
Drug administered at inappropriate site	0	0.00%		
Drug administered to patient of inappropriate age	0	0.00%		
Inappropriate schedule of drug administration	0	0.00%		
Off label use	18	50.0%		
Medication Error	12	33.3%	12	33.3%
Accidental drug intake by child	0	0.0%		
Counterfeit drug administered	0	0.0%		
Drug administered to patient of inappropriate age	0	0.0%		
Drug administration error	1	2.8%		
Drug dispensing error	1	2.8%		
Drug dose omission	1	2.8%		
Drug label confusion	0	0.0%		
Drug name confusion	0	0.0%		
Drug prescribing error	7	19.4%		
Expired drug administered	1	2. 8%		
Inappropriate schedule of drug administration	0	0.0%		
Incorrect dose administered	0	0.0%		
Incorrect drug administration duration	0	0.0%		
Incorrect drug administration rate	0	0.0%		
Incorrect drug dosage form administered	0	0.0%		
Incorrect route of drug administration	0	0.0%		
Incorrect storage of drug	0	0.0%		
Intercepted drug dispensing error	0	0.0%		
Intercepted drug prescribing error	0	0.0%		
Intercepted medication error	0	0.0%		
Labelled drug-disease interaction medication error	0	0.0%		

(continued)

Table 19: Count of Reported Events of Interest Grouped by TRIG Category: Second Quarter 2012

Events by Category	Q2 2012		Total to Date	
	N	%	N	%
Labelled drug-drug interaction medication error	0	0.0%		
Medication error	0	0.0%		
Multiple use of single-use product	0	0.0%		
Poor quality drug administered	0	0.0%		
Therapy naïve	0	0.0%		
Underdose	0	0.0%		
Wrong drug administered	0	0.0%		
Wrong technique in drug usage process	1	2.8%		
Accidental	0	0.0%	**0**	0.0%
Accidental drug intake by child	0	0.0%		
Accidental exposure	0	0.0%		
Accidental overdose	0	0.0%		
Accidental poisoning	0	0.0%		
Multiple drug overdose accidental	0	0.0%		
Toxicity to various agents	0	0.0%		
Dependence	6	16.7%	6	14.3%
Dependence	0	0.0%		
Drug dependence	0	0.0%		
Drug dependence, antepartum	0	0.0%		
Drug dependence, postpartum	0	0.0%		
Drug Withdrawal Syndrome	3	8.3%		
Polysubstance dependence	0	0.0%		
Withdrawal syndrome	3	8.3%		
Drug Diversion	18	50.0%	18	50.0%
Drug diversion	0	0.0%		
Off label use	18	50%		
Respiratory Depression (Symptom)	1	N/A	1	N/A
Acute central respiratory depression SMQ	*1*	*N/A*		

A data mining (disproportionality) analysis was also performed on the selected AERS cases, using the entire AERS database as the background denominator. Not surprisingly, relatively robust signals of disproportionate reporting were generated for the PTs of Interest: "Off label Use" and "Drug prescribing error. A weaker signal was generated for the PT of Interest "Drug withdrawal syndrome". These are known adverse events for TIRF medicines, and are the

subject of the TIRF REMS Access program. When analyzed according to TRIG Categories of Interest, relatively robust signals were also generated for “Inappropriate use,” “Drug diversion,” “Medication error,” and “Drug dependence.” When examined by MedDRA SMQ, the SMQ “Drug abuse, dependence and withdrawal” generated a somewhat weak signal of disproportionate reporting.

Data mining results for these adverse events will continue to be monitored over time to understand the impact of the REMS program on the overall reporting rates for these events of interest.

7.2 American Association of Poison Control Centers (AAPCC)

The AAPCC database is monitored to identify reports of misuse, abuse, and overdose. The AAPCC database includes all 57 poison centers in the US. Reports were requested from AAPCC on calls related to the aggregated data for the class of immediate-release transmucosal fentanyls (no manufacturer names or brand names are provided). The search also included reports of unknown manufacturer oral immediate release fentanyl products, and "unknown fentanyls" with oral and/or inhalation/nasal route(s) of exposure. AAPCC listings of reports for TIRF medicines and unknown fentanyl are presented in Appendix 11.2.

In the prior reporting period (28 December 2011 to 27 April 2012), the AAPCC received reports for 9 cases of known exposure to oral fentanyl immediate-release medicines during the current reporting period. The 9 cases had medical outcomes of 1 major effect, 1 moderate effect, 5 minor effects, 1 unable to follow/judged as potentially toxic exposure, and 1 not followed/judged as non toxic exposure. “Effect” is defined as sign, symptom, or laboratory abnormality and described as minor, moderate, major, or death (See Appendix 11.2 for effect definitions). Eight cases of exposure to unknown fentanyl were reported to the AAPCC during the previous reporting period. The cases had medical outcomes of 1 death (indirect report), 2 major effects, 1 moderate effect, 3 unable to follow/judged as potentially toxic exposure, and 1 not followed/minimal clinical effect possible.

In the current reporting period (28 April 2012 to 28 October 2012), the AAPCC received reports for 11 cases of known exposure to oral fentanyl immediate-release medicines during the current reporting period. The 11 cases had medical outcomes of 1 major effect, 1 moderate effect, 3 minor effects, 2 no follow-up minimal toxicity, and 3 no effects.

Twelve cases of exposure to unknown fentanyl were reported to the AAPCC during the current reporting period. The cases had medical outcomes of 7 deaths (indirect reports), 2 moderate effects, 1 minor effect, 1 unable to follow/judged as potentially toxic exposure, and 1 no effect. Of the 7 deaths, 6 were intentional abuse and 1 had an unknown reason for exposure. The 2 moderate reports were characterized as intentional suspected suicide and the 1 minor event was intentional. The other 2 reports were unintentional

The following tables (Tables 20-26) include reports for exposures to TIRF medicines received between 28 April 2012 and 28 October 2012. The tables do not include reports for unknown fentanyls.

Human Exposure Cases: Site of Call/Site of Exposure

As shown in Table 20 for the current reporting period, of the 11 human exposures associated with TIRF medicines reported, 4 call sites were from a residence (own or other) but there were 10 cases where the site of exposure actually occurred at a residence (own or other). Another 5 calls were made from a health care facility and 2 from "other." Beyond residences, 1 exposure occurred in a school.

Table 20: Site of Call and Site of Exposure, Human Exposure Cases Associated with TIRF Medicines: 28 April 2012 to 28 October 2012

Site	Site of Caller Case Count	Site of Exposure Case Count
Health Care Facility	5	0
Other	2	0
Other Residence	0	1
Own Residence	4	9
Public Area	0	0
Restaurant/food service	0	0
School	0	1
Unknown	0	0
Workplace	0	0
Total	**11**	**11**

Source: AAPCC Table 2

Human Exposure Cases: Age and Gender Distribution

The age and gender distribution of human exposures associated with TIRF medicines is outlined in Table 21. Children ≤2 years of age were involved in 2 exposures and children aged 3 to 19 were involved in 1 exposure. Another 8 exposures were reported in adults ≥30 years of age.

Table 21: Age and Gender Distribution of Human Exposures Associated with TIRF Medicines: 28 April 2012 to 28 October 2012

Age (yr)	Male N (%)	Female N (%)	Unknown N (%)	Total N (%)
1	0	1 (16.7%)	0	1 (9.1%)
2	0	1 (16.7%)	0	1 (9.1%)
3-19	1 (20.0%)	0	0	1 (9.1%)
20-29	0	0	0	0
30-39	1 (20.0%)	0	0	1 (9.1%)
40-49	1 (20.0%)	1 (16.7%)	0	2 (18.2%)
50-59	2 (40.0%)	3 (50.0%)	0	5 (45.5%)
60-69	0	0	0	0
Total	**5 (45.5%)**	**6 (54.5%)**	**0**	**11 (100.0%)**

Source: AAPCC Table 3a

All fatalities – All Ages and Gender

No fatalities were reported in the AAPCC data associated with TIRF medicines (AAPCC Database Table 4).

Human Exposure Cases: Number of Substances

As shown in Table 22, a single substance was implicated in 6 reported human exposures, and 5 patients were exposed to two or more drugs or products including 1 patient who was exposed to 9 substances. There were no exposure- related fatalities. For cases that involved multiple substances, the route of exposure is only captured for one of the substances; therefore, the reported case may include fentanyls that are not oral or inhalation formulations and may not be limited to the class of immediate-release fentanyls.

Table 22: Number of Substances Involved in Human Exposure Cases Associated with TIRF Medicines or a Fentanyl with Oral or Inhalation as Route of Exposure: 28 April 2012 to 28 October 2012

Number of Substances	Case Count N (%)	Fatality Case Count[a] N (%)
1	6 (54.5%)	0
2	1 (9.1%)	0
3	2 (18.2%)	0
4	0	0
5	1 (9.1%)	0
6	0	0
7	0	0
8	0	0
9	1 (9.1%)	0
Total	**11 (100.0%)**	**0**

[a] Includes cases with relative contribution to fatality of 1-Undoubtedly responsible, 2-Probably responsible, or 3-Contributory. This excludes reports with outcome of Death INDIRECT.
Source: AAPCC Table 5

Reason for Exposure

The reasons for both unintentional (general and misuse) and intentional (abuse, suspected suicide, and unknown) human exposures associated with TIRF medicines are shown in Table 23.

Table 23: Reason for Human Exposure Cases Associated with TIRF Medicines: 28 April 2012 to 28 October 2012

Reason Category	Case Count N (%)
Unintentional	
Unintentional - General	2 (50.0%)
Unintentional - Therapeutic error	2 (50.0%)
Subtotal	**4 (36.4%)**
Intentional	
Intentional - Abuse	1 (14.3%)
Intentional - Misuse	2 (28.6%)
Intentional - Suspected suicide	3 (42.9%)
Intentional - Unknown	1 (14.3%)
Subtotal	**7 (63.6%)**
Total	**11 (100.0%)**

Source: AAPCC Table 6a.

Therapeutic Errors

There were 2 reports of therapeutic errors associated with TIRF medicines in the current reporting period (AAPCC Database Table 6B) as shown in Table 24. The therapeutic errors included incorrect dosing route and wrong medication taken/given in patients >19 years of age.

Table 24: Distribution of Therapeutic Errors[a] by Age Associated with TIRF Medicines: 28 April 2012 to 28 October 2012

Scenario	<6 years (Row %)	6-12 years (Row %)	13-19 years (Row %)	>19 years (Row %)	Unknown Child (Row %)	Unknown Adult (Row %)	Unknown (Row %)	Total
Incorrect Dosing Route	0	0	0	1 (100.0%)	0	0	0	1
Dispensing Cup Error	0	0	0	0	0	0	0	0
10-Fold Dosing Error	0	0	0	0	0	0	0	0
Inadvertently Took/Given Someone Else's Medication	0	0	0	0	0	0	0	0
Inadvertently Took/Given Medication Twice	0	0	0	0	0	0	0	0
Incorrect Formulation or Concentration Given	0	0	0	0	0	0	0	0
Incorrect Formulation or Concentration Dispensed	0	0	0	0	0	0	0	0
Wrong Medication Taken/Given	0	0	0	1 (100.0%)	0	0	0	1
Health Professional Iatrogenic Error	0	0	0	0	0	0	0	0
Exposure Through Breast Milk	0	0	0	0	0	0	0	0
More Than One Product Containing Same Ingredient	0	0	0	0	0	0	0	0
Medication Doses Given/Taken Too Close Together	0	0	0	0	0	0	0	0
Confused Units Of Measure	0	0	0	0	0	0	0	0
Other Incorrect Dose	0	0	0	0	0	0	0	0
Drug Interaction	0	0	0	0	0	0	0	0
Other/Unknown Therapeutic Error	0	0	0	0	0	0	0	0

[a] All cases with a scenario category of therapeutic error regardless of reason.

Source: AAPCC Table 6b.

Reason of Exposure by Age

Intentional and unintentional exposures by age are shown in Table 25. Adults >19 years of age accounted for 8 human exposures, 6 intentional and 2 unintentional. There was 1 intentional exposure in a teenager 13 to 19 years of age, and 2 unintentional exposures in children <6 years of age.

Table 25: Distribution of Reason for Exposure by Age Associated with TIRF Medicines: 28 April 2012 to 28 October 2012

Reason	<6 years	6-12 years	13-19 years	>19 years	Unknown Child	Unknown Adult	Unknown Age	Missing	Total
Unintentional	2	0	0	2	0	0	0	0	**4**
Intentional	0	0	1	6	0	0	0	0	**7**
Total	**2**	**0**	**1**	**8**	**0**	**0**	**0**	**0**	**11**

Source: AAPCC Table 7

Reason of Exposure by Age for Fatalities

There were no reports of unintentional fatalities from exposure to TIRF medicines (AAPCC Database Table 8).

Route of Exposure

Ingestion was the route of exposure in 11 of 11 cases associated with TIRF medicines (Table 26). Each exposure case may have more than one route

Table 26: Route of Exposure for Human Exposure Cases: 28 April 2012 to 28 October 2012

Route	Human Exposures	Fatal Exposures[a]
Ingestion	11	0
Total[b]	**11**	**0**

[a] Includes cases with relative contribution to fatality of 1-Undoubtedly responsible, 2-Probably responsible, or 3-Contributory. This excludes reports with outcome of Death INDIRECT.

[b] Each exposure case may have more than one route.

Source: AAPCC Table 9

Medical Outcome

Table 27 displays the medical outcome of human exposure cases associated with TIRF medicines distributed by age. A greater number of severe medical outcomes was observed in the older age groups.

Table 28 compares medical outcome and reason for exposure and shows a higher frequency of serious outcomes in intentional (n=7) versus unintentional exposures (n=4).

Table 27: Medical Outcome of Human Exposure Cases by Patient Age: 28 April 2012 to 28 October 2012

Outcome	<6 years N (%)	6-12 years N (%)	13-19 years N (%)	>19 years N (%)	Unknown Child N (%)	Unknown Adult N (%)	Unknown Age N (%)	Total N (%)
No effect	1 (50.0%)	0	0	2 (25.0%)	0	0	0	3 (27.3%)
Minor effect	1 (50.0%)	0	0	3 (37.5%)	0	0	0	4 (36.4%)
Moderate effect	0	0	1 (100.0%)	0	0	0	0	1 (9.1%)
Major effect	0	0	0	1 (12.5%)	0	0	0	1 (9.1%)
Death	0	0	0	0	0	0	0	0
No follow-up, nontoxic	0	0	0	0	0	0	0	0
No follow-up, minimal toxicity	0	0	0	2 (25.0%)	0	0	0	0
No follow-up, potentially toxic	0	0	0	0	0	0	0	0
Unrelated effect	0	0	0	0	0	0	0	0
Confirmed nonexposure	0	0	0	0	0	0	0	0
Death, indirect report	0	0	0	0	0	0	0	0
Total	**2 (18.2%)**	**0**	**1 (9.1%)**	**8 (72.7%)**	**0**	**0**	**0**	**11 (100.0%)**

Source: AAPCC Table 11

Table 28: Medical Outcome by Reason for Exposure in Human Exposures: 28 April 2012 to 28 October 2012

Outcome	Unintentional N (%)	Intentional N (%)	Other N (%)	Unknown N (%)	Total N (%)
No effect	2 (50.0%)	1 (14.3%)	0	0	3 (27.3%)
Minor effect	1 (25.0%)	3 (42.9%)	0	0	4 (36.4%)
Moderate effect	0	1 (14.3%)	0	0	1 (9.1%)
Major effect	0	1 (14.3%)	0	0	1 (9.1%)
Death	0	0	0	0	0
No follow-up, nontoxic	0	0	0	0	0
No follow-up, minimal toxicity	1 (25.0%)	1 (14.3%)	0	0	2 (18.2%)
No follow-up, potentially toxic	0	0	0	0	0
Unrelated effect	0	0	0	0	0
Confirmed nonexposure	0	0	0	0	0
Death, indirect report	0	0	0	0	0
Total	**4 (36.4%)**	**7 (63.6%)**	**0**	**0**	**11 (100.0%)**

Source: AAPCC Table 12

8 PERIODIC SURVEYS OF STAKEHOLDERS

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess patients' and caregivers,' pharmacists, and prescribers knowledge, attitudes, and behavior (KAB) regarding the safe use of TIRF medicines as described in the educational materials of all stakeholders, enrollment form (pharmacists and prescribers only) and Prescribing Information (pharmacists and prescribers only) of each product. The protocols describe the administration of the individual surveys that were conducted among patients, pharmacists, and prescribers who are treated with TIRF medicines, or their caregivers (see Appendix 11.4.1, 11.4.2, and 11.4.3, respectively, for the patient, pharmacist, and prescriber survey protocols).

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 are implemented so that data are available for inclusion in the REMS Assessment Reports 12 months after approval of the TIRF REMS and annually thereafter.

8.1 Patient KAB Survey

8.1.1 Survey Statistics

Based on the number of prescriptions filled during the 90 days prior to 12 September 2012, the national pharmacy chain network partner identified 1112 possible participants among patients and caregivers. All of these possible participants were sent a survey invitation letter. A total of 899 follow up letters were sent to non-responders on 08 October 2012. Of the 1112 possible participants, 198 respondents indicated interest in the survey and were screened for eligibility to participate and 192 respondents met eligibility criteria and completed the survey. Of these 192 respondents, 112 (56.6%) completed the survey online, and 80 (40.4%) completed it by telephone.

Although, the survey had a target of 300 eligible completed responders, the initial population of 1112 possible participants was small. The response of 192 completed surveys is within the expected response rate (10%) to mailed invitations. To increase participation in the survey, recruitment methodology and inclusion criteria will be evaluated in future survey waves.

Of the 198 respondents, the screening procedure identified 192 eligible participants (including 190 patients and 2 caregivers) all of whom completed the survey. Due to the small number of caregivers participating in the survey, the majority of results are reported for patients and caregivers combined.

8.1.2 Demographics and Respondent Characteristics

The majority of respondents were above the age of 40 years (88.0%), female (63.0%), and had at least some college or Associate's degree or higher education (153, 79.7%). Participants were largely from the Midwest (32.3%) or South (39.6%) with the Northeast accounting for 13.5% and the West 14.0% of the respondents.

8.1.3 TIRF Educational Materials

Most respondents, 173 (90.1%), reported they received a Medication Guide for the TIRF medicine prescribed to them. Of these 173 respondents, 158 (91.3%) received the Medication Guide from the pharmacy; 167 (96.5%) read the Medication Guide of those who read it, 109 (65.3%) read all of it and 41 (24.6%) most of it. From these 167 respondents, 96 (57.5%) understood all of the Medication Guide and 58 (34.7%) most of it.

When asked if they had received, read, and understood the Patient-Prescriber Agreement Form (PPAF), 134 (69.8%) respondents confirmed that someone at the doctor's office offered to explain the PPAF to them, and that 113 (84.3%) of them understood all of it and 19 (14.2%) understood most of it. The PPAF was signed by 144 (75.0%) respondents; of these 144 responders, 113 reported receiving a copy of the signed PPAF.

8.1.4 Patient Survey Results

The specific goals of the TIRF medicines patient KAB survey were to evaluate the level of knowledge and assess the attitudes and behavior of patients and 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.

8.1.4.1 Key Risk Message 1

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

Analysis of responses to Question 12d for Key Risk Message 1 showed that 90.1% of the respondents were aware of the risk of life-threatening breathing problems with TIRF medicines.

8.1.4.2 Key Risk Message 2

Key Risk Message 2 refers to the respondents' knowledge that they should not take TIRF Medicines if they are not opioid tolerant. Three questions define this key risk message.

In response to the statement in Question 10 that TIRF medicines should only be taken by patients who are opioid tolerant, 90.6% respondents gave the correct (true) response.

The majority of respondents 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 (91.7%), and the majority also understood that it is not okay for patients to-take TIRF medicines for headache pain (70.8%).

Evidence of understanding this key risk information is further supported by the average number of 2.5 out of a possible 3 correct responses.

8.1.4.3 Key Risk Message 3

Key Risk Message 3 refers to the patient's knowledge that TIRF medicines should be taken exactly as prescribed by the healthcare provider. Three questions define this key risk message).

Less than half (42.7%) of respondents understood that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine. However, all patients (100%) understood that TIRF medicines should be taken exactly as prescribed by the doctor and 82.3% of respondents knew that is not OK to take TIRF medicines for short-term pain that will go away in a few days. Evidence of understanding this key risk information is further supported by the average number of 2.3 out of a possible 3 correct responses.

8.1.4.4 Key Risk Message 4

Key Risk Message 4 refers to the patient's knowledge that they must not switch TIRF medicines without talking to a healthcare provider.

The majority of respondents (96.9%) understood that it is not safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.

8.1.4.5 Key Risk Message 5

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

All (100%) respondents understood that a patient may not give TIRF medicines to another person if they have the same symptoms as the patient, and 97.9% understood that selling or giving away TIRF medicines is against the law.

Evidence of understanding this key risk information is further supported by the average number of 2.0 out of a possible 2 correct responses.

8.1.4.6 Key Risk Message 6

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

All (100%) respondents understood that TIRF medicines should be stored in a safe place out of the reach of children. The majority of respondents understood that TIRF medicines must be disposed of as described in the specific product's Medication Guide (95.8%); a TIRF medicine can cause an overdose and death in any child who takes it (90.6%); and that they should get emergency help right way (89.1%) when asked, "What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine?"

Evidence of understanding this key risk information is further supported by the average number of 3.8 out of a possible 4 correct responses.

8.1.5 Additional Safety Questions about TIRF Medicines Safety

Respondents answered additional questions beyond those associated with the key risk messages. These questions assessed whether the patient had been informed of the risks and possible side effects, indications, usage, and storage, and the availability of TIRF medicines through the TIRF REMS Access program.

Most respondents (67.7% to 89.6%) were aware of the clinical conditions for using TIRF medicines; however, the awareness was low regarding use in chronic non-cancer pain with only 24.5% of respondents correctly responding false.

The majority of patients were told by their doctor, nurse, or other healthcare provider how to use their TIRF medicine (93.8%) and how to properly store the medicine (80.7%). Half (50.5%) of all patients understood that TIRF medicines are only available through the TIRF REMS Access program.

8.2 Pharmacy KAB Survey

8.2.1 Survey Statistics

A total of 7236 pharmacists were invited to participate in this survey. Of those invited to participate, 6286 were outpatient pharmacists, 650 were inpatient pharmacists, and 300 were pharmacists practicing in Closed System Pharmacies (CSPs). In order to increase the total overall response, 98 out bound calls were made from 09 October 2012 to 11 October 2012. Reminder invitations were sent to potential participants to reduce volunteer bias. Some pharmacists received more than 1 reminder.

In all, a total of 302 pharmacists met eligibility criteria and completed the survey. Of these 302 pharmacists, 286 (94.7%) completed the survey online, and 16 (5.3%) completed it by telephone.

From the 302 respondents, 304 surveys were collected. It was identified that 2 respondents completed the survey twice. Only the first completed survey was included in the analysis for

each respondent. Of the 302 pharmacists who completed the survey, 6 were CSP pharmacists, 16 were inpatient pharmacists, and 280 were outpatient pharmacists.

A total of 348 pharmacists agreed to participate in this survey and 304 of these pharmacists worked in pharmacies that were enrolled in the TIRF REMS. Of the 348 total respondents, 44 were ineligible to participate in the survey because they worked in pharmacies that were not enrolled or they did not know whether their pharmacy was enrolled in the TIRF REMS. Of the 304 respondents who reported that their pharmacies were enrolled in the TIRF REMS Access Program, one respondent was ineligible for the survey because the respondent, or an immediate family member, had worked for a TRIG company in the past, and one respondent did not know whether he/she or an immediate family member had worked for a TRIG company, UBC, Specialty Care Solutions, RelayHealth, or FDA in the past.

8.2.2 Demographic and Respondent Characteristics

The majority of eligible respondents who completed the survey were male (66.9%). Respondents from the South, Northeast, and Midwest reflected 34.4%, 26.5%, and 21.5% of total respondents, respectively, while respondents from the Western region of the US composed 17.2%, of the total survey population. The proportion of eligible completed pharmacists within each geographic region was similar to the overall proportion of pharmacists (37,480 pharmacists enrolled in the TIRF REMS Access Program as of 15 August 2012) in each geographic region. Almost half (48.0%) had been a practicing pharmacist for more than 15 years.

The majority of pharmacists (82.1%) functioned as the pharmacist in charge for the TIRF REMS Access Program where they worked. Most pharmacists (74.2%) had dispensed a TIRF medicine zero to 2 times per month within the past 6 months, and had dispensed Actiq or generic Actiq most frequently within the 6 months prior to taking the survey (76.7%).

8.2.3 TIRF Educational Materials

Pharmacists were asked about their access to educational materials for TIRF medicines, specifically the Full Prescribing Information and the Medication Guide. Most respondents reported they received or had access to the Full Prescribing Information and the Medication Guide (97.7% and 97.0%, respectively). Of those with access to these materials, 75.3% and 82.9%, respectively, indicated that they had read the Full Prescribing Information and the Medication Guide.

8.2.4 Pharmacy Survey Results

The TIRF medicines pharmacist KAB survey is a systematic approach to measuring knowledge, attitudes, and behaviors associated with the prescribing of TIRF medicines and risks associated with its use.

8.2.4.1 Key Risk Message 1

Key Risk Message 1 refers to the pharmacist's knowledge of the specific contraindications for TIRF medicines in patients.

Analysis of responses to components of Question 6 for Key Risk Message 1 showed that a high percentage of pharmacists know that TIRF medicines are contraindicated in opioid non-tolerant patients (86.1%) and that death has occurred in opioid non-tolerant patients treated with some fentanyl products (92.1%). Most pharmacists were aware patients just starting a TIRF medicine must begin with titration from the lowest available dose for that product (78.5%) and that TIRF medicines may not be used to treat opioid non-tolerant patients (78.5%). Evidence for understanding of this key risk information is further supported by the average number of 3.4 out of 4 correct responses.

8.2.4.2 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 8 for Key Risk Message 2 indicate that most pharmacists were aware TIRF medicines are prescribed for adult opioid-tolerant patients with breakthrough pain from cancer (83.4%) and not for patients with acute or postoperative pain (78.1%), headache or migraine pain (89.1%), or dental pain (94.7%). Evidence for understanding of this key risk information is further supported by an average number of 3.5 out of 4 correct responses.

8.2.4.3 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 6, 7, and 9 for Key Risk Message 3 showed that a high percentage of pharmacists were aware that it is important to monitor for signs of abuse and addiction in patients who take TIRF medicines (97.7%), 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 (99.7%), and that TIRF medicines can be abused in a manner similar to other opioid agonists (90.4%). More than half of pharmacists were aware that a personal history of psychiatric illness is a risk factor for opioid abuse (66.6%). Evidence for understanding of this key risk information is further supported by an average number of 3.5 out of 4 correct responses.

8.2.4.4 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 9 for Key Risk Message 4 showed that a high percentage of pharmacists understood TIRF medicines are not interchangeable with each other regardless of the route of administration (95.0%), the conversion of one TIRF medicine to another may result in a fatal overdose (92.7%), and dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (92.4%). Evidence for understanding of this key risk information is further supported by an average number of 2.8 correct responses out of 3.

8.2.5 Additional Safety Questions about TIRF Medicines Safety

Despite the high proportion of pharmacists responding correctly to the questions around Key Risk Message 1 (i.e., that patients must be opioid tolerant), only 12.6% of pharmacists correctly indicated that patients considered opioid tolerant are those who are taking regular opioid therapy for 1 week or longer. Additionally, 15.6% correctly indicated that patients not currently taking opioid therapy but who have no known intolerance or hypersensitivity to fentanyl are not considered opioid tolerant. In contrast a high percentage (80.1%) correctly indicated patients not currently taking opioid therapy but who had taken opioid therapy before are not considered opioid tolerant. Because the results for the 2 components of Question 5 are discrepant from the other pharmacist results around opioid tolerance, it is possible that these results reflect a misunderstanding of the question rather than a lack of understanding of the important safety information. Additional research will be conducted to explore pharmacists' interpretation and understanding of all 3 components of Question 5. The outcome of the research will be included in the next assessment report, and action proposed, if appropriate.

8.2.6 Pharmacist Activities When Dispensing TIRF Medicines

More than half of the pharmacists indicated they always give patients (or their caregivers) the Medication Guide for TIRF medicine (90.1%), instruct the patient (or their caregivers) not to share TIRF medicines (66.9%), counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal (62.9%), instruct patients (or their caregivers) to keep TIRF medicines out of reach of children (68.9%), and instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines (57.0%). Almost half (48.3%) always ask patients (or their caregivers) about the presence of children in the home, but 22.5% ask only with the first prescription.

8.3 Prescriber KAB Survey

8.3.1 Survey Statistics

A total of 5330 prescribers were sent letters inviting them to participate in this survey. An additional 3505 reminder letters were sent. Prescribers may have received more than 1 reminder letter.

In all, a total of 302 prescribers met the eligibility criteria, and completed the survey. Of these 302 prescribers, 293 (97.0%) completed the survey online, and 9 (3.0%) completed it by telephone.

A total of 358 prescribers agreed to participate in this survey and of those 315 prescribers were enrolled in the TIRF REMS Access program; 43 prescribers were ineligible because they were not enrolled in the program or they did not know whether they were enrolled. Eleven respondents were ineligible for the survey because they, or an immediate family member, had worked for UBC or a TRIG company in the past, or did not know whether they, or an immediate family member, had worked for a TRIG company, UBC, RelayHealth, McKesson Specialty Care Solutions, or FDA in the past, and 2 prescribers preferred not to answer.

8.3.2 Demographics and Respondent Characteristics

The majority of respondents were male (59.6%). Respondents from the South, West, and Northeast included 31.1%, 26.8%, and 25.2% of the survey population, respectively; while respondents from the Midwest region of the US composed 16.9%, of the total survey population. The proportion of eligible completed prescribers within each geographic region was similar to the overall proportion of prescribers (7701 prescribers enrolled in the TIRF REMS Access program as of 15 August 2012) in each geographic region. The most common healthcare degree was an MD (57.0%), and the most common medical specialties were pain management (50.7%) and oncology (22.5%). Of respondents who were medical doctors, most respondents (50.7%) had practiced medicine for more than 15 years.

Of prescribers who described their medical specialty as 'other,' the majority (5.0%) stated their medical specialty was General Medicine, followed by Neurology and Rehabilitation (5% each).

Nearly half (46.7%) of the prescribers prescribed TIRF medicines 1 to 2 times a month within the past 6 months, and Actiq or generic Actiq was most frequently prescribed TIRF medicine (79.6% of prescribers).

8.3.3 TIRF Educational Materials

Prescribers were asked about their awareness of educational materials for TIRF medicines, specifically the Full Prescribing Information, the Medication Guide, and the PPAF. Most respondents received or had access to the Full Prescribing Information and the Medication Guide (94.4% and 90.4%, respectively). Of those with access to these materials, 80.0% and 89.0%, respectively, indicated that they had read the Full Prescribing Information and the Medication Guide. Additionally, most prescribers review the PPAF with each patient or their caregiver (88.1%), and, following review, the majority of those prescribers (94.0%) sign and have the patient/caregiver sign the form, and 82.5% give a copy of the PPAF to the patient or their caregiver.

8.3.4 Prescriber Survey Results

8.3.4.1 Key Risk Message 1

Key Risk Message 1 assesses the prescriber's knowledge of the specific contraindications for TIRF medicines in patients.

Analysis of responses to components of Question 6 for Key Risk Message 1 showed that a high percentage of prescribers know that TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur (87.4%) and that death has occurred in opioid non-tolerant patients treated with some fentanyl products (95.7%). Most prescribers were aware patients just starting a TIRF medicine must begin with titration from the lowest available dose for that product (83.1%) and that TIRF medicines may not be used to treat opioid non-tolerant patients (82.5%). This is further supported by an average number of correct responses of 3.5 out of 4.

8.3.4.2 Key Risk Message 2

Key Risk Message 2 assesses the prescriber's knowledge of the approved indications for prescribing TIRF Medicines to opioid tolerant patients.

Responses to components of Question 8 for Key Risk Message 2 indicate that a high percentage of prescribers were aware TIRF medicines are prescribed for adult opioid-tolerant patients with breakthrough pain from cancer (95.4%) and not for patients with acute or postoperative pain (86.4%), headache or migraine pain (86.8%),or dental pain (96.0%). This is further supported by an average number of correct responses of 3.6 out of 4.

8.3.4.3 Key Risk Message 3

Key Risk Message 3 assesses the prescriber's knowledge of the risk factors and signs and symptoms of opioid abuse in patients who take TIRF medicines.

Responses to components of Questions 6, 7, and 9 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 (99.7%), a personal history of psychiatric illness is a risk factor for opioid abuse (82.5%), 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 (99.3%), and that TIRF medicines can be abused in a manner similar to other opioid agonists (97.7%). This is further supported by an average number of correct responses of 3.8 out of 4.

8.3.4.4 Key Risk Message 4

Key Risk Message 4 assesses the prescriber's knowledge that TIRF medicines are not interchangeable regardless of the route of administration. .

Responses to components of Question 9 for Key Risk Message 4 showed that a high percentage of prescribers understood TIRF medicines are not interchangeable with each other regardless of

the route of administration (95.7%), the conversion of one TIRF medicine to another may result in a fatal overdose (94.7%), and dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (90.4%). This is further supported by an average number of correct responses of 2.8 out of 3.

8.3.5 Additional Questions About TIRF Medicines Safety

Despite the high proportion of physicians responding correctly to the questions around Key Risk Message 1 (i.e. that patients must be opioid tolerant), only 7.9% of prescribers correctly indicated that patients considered opioid tolerant are those who are taking regular opioid therapy for one week or longer. Additionally, 15.6% correctly indicated patients not currently taking opioid therapy but who have no known intolerance or hypersensitivity to fentanyl are not considered opioid tolerant. In contrast a high percentage (88.7%) correctly indicated patients not currently taking opioid therapy but who had taken opioid therapy before are not considered opioid tolerant.

Because the results for the 2 components of Question 5 are discrepant from the other prescriber results around opioid tolerance, it is possible that these results reflect a misunderstanding of the question rather than a lack of understanding of the educational materials. Additional research will be conducted with survey respondents to explore their interpretation and understanding of all 3 components of Question 5. The outcome of the research will be included in the next assessment report, and based on the outcome appropriate action may be taken, such as rephrasing Question 5.

8.3.6 Prescriber Activities When Prescribing TIRF Medicines

Prescribers were asked about specific activities performed when prescribing TIRF medicines.

More than half of prescribers indicated they always ask patients (or their caregivers) about the presence of children in the home (57.9%), instruct patients (or their caregivers) not to share TIRF medicines (79.1%), counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal (65.9%), instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children (72.8%), instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines (60.9%).

Less than half of prescribers (40.4%) always give patients (or their caregivers) the Medication Guide for their TIRF medicine, but 42.4% give their patients (or their caregivers) the Medication Guide for their TIRF medicine with the first prescription.

8.4 Overall Conclusions for KAB Results

Patients:

The analyses of responses to questions defining each of the six key risk messages demonstrated that most respondents were well informed about the risks and safe use criteria associated with TIRF medicines.

Overall, this patient survey shows that the ongoing patient-oriented educational process is meeting its objectives in that the majority of patients completing the survey were aware of the key issues related to their use of a TIRF medication.

Pharmacists and Prescribers:

Among responses to all questions about the safe use of TIRF medicines, there were two questions relating to the definition of a non-opioid tolerant patient that had low correct response rates for both pharmacist and prescribers. A minority of prescribers and pharmacists correctly indicated that patients considered opioid tolerant are those who are taking regular opioid therapy for one week or longer (12.6% pharmacists and 7.9% prescribers). Few prescribers and pharmacists correctly indicated patients not currently taking opioid therapy but who have unknown intolerance or hypersensitivity to fentanyl are not considered opioid tolerant (15.6%, for prescribers and pharmacists). Because both pharmacists and prescribers had low correct response rates for both of these questions, and because the high correct response rates for the other related risk messages, including other questions about opioid tolerance, this may possibly indicate a challenge in understanding the questions and not a knowledge issue. Additional research will be conducted to explore these results. The outcome of the research will be included in the next assessment report, and, based on the outcome, appropriate action may be taken.

Across the surveys for all key risk messages both pharmacists and prescribers demonstrated a high level of understanding that TIRF medicines are contraindicated in opioid non-tolerant patients, are only indicated for the management of breakthrough pain in adult patients with cancer, contain fentanyl with abuse liability similar to other opioid analgesics, and are not interchangeable with each other regardless of route of administration.

9 FDA COMMUNICATIONS

During this reporting period, 2 letters and multiple modified PPAFs were received by the TIRF REMS Access program (see Section 6, ID#1). The TRIG shared this feedback from prescribers with the FDA.

10 POST-APPROVAL STUDIES AND CLINICAL TRIALS

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

11 OVERALL CONCLUSIONS

The TIRF REMS Access program was successfully launched on 12 March 2012, approximately 11 weeks after REMS approval. Between 27 April 2012 and 28 October 2012, prescribers,

patients, and pharmacies were transitioned from individual REMS programs and 8747 additional stakeholders successfully enrolled in the TIRF REMS Access program.

With an overall volume of more than 54,614 prescriptions authorized for REMS edits, there were few reports of patients unable to gain access to TIRF medicines or reports of system issues. Only a few instances of un-enrolled physicians prescribing TIRF medicines, un-enrolled pharmacies dispensing, or un-enrolled patients receiving product were identified. A thorough investigation is applied to all of these instances, and, where complete, corrective actions have been documented. The TIRF REMS Access program system continues to be monitored for issues and, where appropriate, corrective actions instituted. Sponsors remain vigilant in monitoring spontaneous reports and external data sources, such as AAPCC, to identify safety risks.

The REMS goal of educating prescribers and pharmacists on the potential for misuse, abuse, addiction, and overdose is being documented through the implementation of the Knowledge Assessment, which is required for enrollment. Additional information obtained through the pharmacy and prescriber KAB surveys shows that both pharmacists and prescribers demonstrated a high level of understanding 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 regardless of route of administration. Additional research will be conducted to understand challenges in comprehension of questions with low correct response rates for prescribers and pharmacists. The outcome of this research will be included in the next assessment report, and, based on the outcome, appropriate action may be taken.

Patient education is completed through healthcare provider counseling and completion of a PPAF. The patient KAB survey results showed that the ongoing patient-oriented educational process is meeting its objectives in that the majority of patients completing the survey were aware of the key issues related to their use of a TIRF medication (i.e., not sharing TIRF medicines, taking TIRF medicines as prescribed, and proper disposal of TIRF medicines).

Surveillance methods using AAPCC data identified few reported exposures to poison centers. There were 12 cases of exposure to unknown fentanyl reported to the AAPCC during the current reporting period, including 7 fatalities. There were 11 cases of exposure to known oral fentanyl immediate-release medicines reported to the AAPCC, including 3 pediatric exposures. There were no fatalities reported for exposure to TIRF medicines.

In the US, 36 FDA AERS case reports were associated with a TIRF medicine exposure, of which 27 of the cases included one of the individual PT of Interest for the TIRF REMS or at least one PT from the MedDRA SMQ, *Acute Central Respiratory Depression.* Not surprisingly, relatively robust signals were generated for the PT of Interest: "Off label Use" and "Drug prescribing error." These are known adverse events for TIRF medicines. The FDA AERS

database will be monitored to understand the impact of the TIRF REMS Access program on the rates of these Preferred Terms of Interest.

APPENDICES

11.1 Medical Dictionary for Drug Regulatory Activities (MedDRA) Preferred Terms

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	Multiple drug overdose
Injury, poisoning and procedural complications	Medication errors	Overdoses	Multiple drug overdose accidental
Injury, poisoning and procedural complications	Medications errors	Overdoses	Multiple drug overdose intentional
Injury, poisoning and procedural complications	Medication errors	Overdoses	Overdose
Death			
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Accidental death
Nervous system disorders	Neurological disorders NEC	Cortical dysfunction NEC	Brain death
Cardiac disorders	Cardiac arrhythmias	Ventricular arrhythmias and cardiac arrest	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
Cardiac disorders	Cardiac arrhythmias	Ventricular arrhythmias and cardiac arrest	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
Social Circumstances	Family Issues	Bereavement issues	Death of companion
Social Circumstances	Family Issues	Bereavement issues	Death of relative

Primary SOC	High Level Group	High Level Term	Preferred Term
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Sudden unexplained death in epilepsy
Respiratory, thoracic and mediastinal disorders	Respiratory disorders NEC	Breathing abnormalities	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
Misuse			
General disorders and administration site conditions	Therapeutic and nontherapeutic effects (excl toxicity)	Withdrawal and rebound effects	Medication overuse headache
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Intentional drug misuse
Drug abuse dependence and withdrawal SMQ (Standardized MedDRA Query)			
Abuse			
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug abuse
Social circumstances	Lifestyle issues	Drug and chemical abuse	Drug abuser
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Substance abuse
Social circumstances	Lifestyle issues	Drug and chemical abuse	Substance abuser
Social circumstances	Lifestyle issues	Drug and chemical abuse	Ex-drug abuser
Injury, poisoning and procedural complications	Exposures, chemical injuries and poisoning	Poisoning and toxicity	Substance-induced mood disorder
Injury, poisoning and procedural complications	Exposures, chemical injuries and poisoning	Poisoning and toxicity	Substance-induced psychotic disorder
Drug abuse dependence and withdrawal SMQ (Standardized MedDRA Query)			
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
Surgical and medical procedures	Therapeutic procedures and supportive care	Therapeutic procedures NEC	Off label use
Injury, poisoning and	Medication errors	Maladministrations	Drug administered to patient of

Primary SOC	High Level Group	High Level Term	Preferred Term
procedural complications			inappropriate age
Medication Error			
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Intercepted medication error
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Intercepted drug prescribing error
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Medication error
Injury poisoning and procedural complications	Medication errors	Maladministrations	Counterfeit drug administered
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Drug administration error
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Drug dose omission
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Expired drug administered
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Incorrect dose administered
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Incorrect drug administration duration
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Incorrect drug administration rate
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Incorrect drug dosage form administered
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Incorrect route of drug administration
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Poor quality drug administered
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Inappropriate schedule of drug administration
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Underdose
General disorders and administrative sites	Therapeutic and nontherapeutic effects	Therapeutic and nontherapeutic responses	Therapy naive
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Wrong drug administered
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Wrong technique in drug usage process
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Drug dispensing error
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Drug label confusion
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Drug name confusion

Primary SOC	High Level Group	High Level Term	Preferred Term
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Drug prescribing error
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Incorrect storage of drug
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Intercepted drug dispensing error
Injury, poisoning and procedural complications	Medication errors	Medication monitoring errors	Labelled drug-disease interaction medication error
Injury, poisoning and procedural complications	Medication errors	Medication monitoring errors	Labelled drug-drug interaction medication error
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Drug administered to patient of inappropriate age
Injury, poisoning and procedural complications	Medication errors	Medication errors due to accidental exposures	Accidental drug intake by child
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Multiple use of a single use product
Accidental			
Injury, poisoning and procedural complications	Medication errors	Medication errors due to accidental exposures	Accidental drug intake by child
Injury, poisoning and procedural complications	Medication errors	Medication errors due to accidental exposures	Accidental exposure
Injury, poisoning and procedural complications	Medication errors	Overdoses	Accidental overdose
Injury, poisoning and procedural complications	Chemical injury and poisoning	Poisoning and toxicity	Accidental poisoning
Injury, poisoning and procedural complications	Chemical injury and poisoning	Poisoning and toxicity	Toxicity to various agents
Injury, poisoning and procedural complications	Medication errors	Overdoses	Multiple drug overdose accidental
Dependence			
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Dependence
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug dependence
Pregnancy, puerperium and perinatal conditions	Foetal complications	Foetal conditions due to maternal conditions	Drug dependence, antepartum
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug dependence, postpartum
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Polysubstance dependence
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Withdrawal syndrome
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug withdrawal syndrome

Primary SOC	High Level Group	High Level Term	Preferred Term
Drug Diversion			
Social circumstances	Legal issues	Criminal activity	Drug diversion
Surgical and medical procedures	Therapeutic procedures and supportive care NEC	Therapeutic procedures NEC	Off label use
Respiratory Depression			
Acute central respiratory depression SMQ (Standardized MedDRA Query)			

11.2 AAPCC LISTINGS

The following definitions are used to characterize data in the attached listings of TIRF medicines fentanyl exposures and unknown exposures which were derived AAPCC annual report: Bronstein AC, Spyker DA, Cantilena LR et al. 2010 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th annual report. *Clinical Toxicology*. 2011;49:910-941.

No effect: The patient did not develop any signs or symptoms as a result of the exposure.

Minor effect: The patient developed some signs or symptoms as a result of the exposure, but they were minimally bothersome and generally resolved rapidly with no residual disability or disfigurement. A minor effect is often limited to the skin or mucus membranes (e.g., self-limited gastrointestinal symptoms, drowsiness, skin irritation, first-degree dermal burn, sinus tachycardia without hypotension, and transient cough).

Moderate effect: The patient exhibited signs or symptoms as a result of the exposure that were more pronounced, more prolonged, or more systemic in nature than minor symptoms. Usually, some form of treatment is indicated. Symptoms were not life-threatening, and the patient had no residual disability or disfigurement (e.g., corneal abrasion, acid-base disturbance, high fever, disorientation, hypotension that is rapidly responsive to treatment, and isolated brief seizures that respond readily to treatment).

Major effect: The patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement (e.g., repeated seizures or status epilepticus, respiratory compromise requiring intubation, ventricular tachycardia with hypotension, cardiac or respiratory arrest, esophageal stricture, and disseminated intravascular coagulation).

Death: The patient died as a result of the exposure or as a direct complication of the exposure.

A statement on AAPCC data must be included in all publications referencing AAPCC data. The AAPCC maintains the national database of information logged by the country's 57 poison control centers. Case records in this database are from self-reported calls: they reflect only information provided when the public or healthcare professionals report an actual or potential exposure to a substance (e.g., an ingestion, an inhalation, or a topical exposure, etc.), or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s).

All data produced from the AAPCCs databases during the year in which the exposures occur is considered preliminary. Changes occur in only a small number of cases each year. This is because it is possible that a poison center may update a case anytime during that year if new data is obtained. In the fall of each year the data for the previous year is locked and no changes are permitted. At that time the data for a year is considered closed.

AAPCC Listing of Exposures to Known TRIG TIRF Immediate-Release Oral Medicines												
Subject	Start Date	Public Case Number	Age (yrs)	Gender	Substance Rank	No of Substances	Formulation	Quantity	Quantity Unit	Major Category	Reason For Exposure	Medical Outcome
1	5/3/12	31874263522012	55	Female	3	3	Solid (tablets / capsules / caplets)	NULL	Unknown	Fentanyl	Intentional - Suspected suicide	No effect
	5/3/12	31874263522012	55	Female	1	3	Solid (tablets / capsules / caplets)	10.8	g	Other Types of Anticonvulsant (Excluding Barbiturates)	Intentional - Suspected suicide	No effect
	5/3/12	31874263522012	55	Female	2	3	Solid (tablets / capsules / caplets)	19	mg	Benzodiazepines	Intentional - Suspected suicide	No effect
2	7/9/12	1488183362012	59	Female	1	1	Other	1	each (e.g. bites / stings)	Fentanyl	Intentional - Misuse	Not followed, minimal clinical effects possible (no more than minor effect possible)
3	7/13/12	19228193742012	45	Male	1	1	Solid (tablets / capsules / caplets)	16	tabs / pills / capsules	Fentanyl	Intentional - Misuse	Minor effect
4	7/19/12	22802523012012	32	Male	1	3	Solid (tablets / capsules / caplets)	2	tabs / pills / capsules	Fentanyl	Unintentional - Therapeutic error	Not followed, minimal clinical effects possible (no more than minor effect possible)
	7/19/12	22802523012012	32	Male	2	3	Solid (tablets / capsules / caplets)	2	tabs / pills / capsules	Beta Blockers (Including All Propranolol Cases)	Unintentional - Therapeutic error	Not followed, minimal clinical effects possible (no more than minor effect possible)
	7/19/12	22802523012012	32	Male	3	3	Solid (tablets / capsules / caplets)	2	tabs / pills / capsules	Nitroglycerin	Unintentional - Therapeutic error	Not followed, minimal clinical effects possible (no more than minor effect possible)
5	7/26/12	729172193542012	2	Female	1	1	Other	100	mcg	Fentanyl	Unintentional - General	No effect
6	7/29/12	4724053302012	57	Male	3	9	Other	NULL	Unknown	Fentanyl	Intentional - Suspected suicide	Minor effect
	7/29/12	4724053302012	57	Male	1	9	Solid (tablets / capsules / caplets)	NULL	Unknown	Colchicine	Intentional - Suspected suicide	Minor effect
	7/29/12	4724053302012	57	Male	2	9	Solid (tablets / capsules / caplets)	NULL	Unknown	Acetylsalicylic Acid Alone, Adult Formulations	Intentional - Suspected suicide	Minor effect
	7/29/12	4724053302012	57	Male	4	9	Solid (tablets / capsules / caplets)	NULL	Unknown	Long-Acting Nitrates	Intentional - Suspected suicide	Minor effect
	7/29/12	4724053302012	57	Male	5	9	Solid (tablets / capsules / caplets)	NULL	Unknown	Thiazide	Intentional - Suspected suicide	Minor effect

AAPCC Listing of Exposures to Known TRIG TIRF Immediate-Release Oral Medicines												
Subject	Start Date	Public Case Number	Age (yrs)	Gender	Substance Rank	No of Substances	Formulation	Quantity	Quantity Unit	Major Category	Reason For Exposure	Medical Outcome
	7/29/12	4724053302012	57	Male	6	9	Solid (tablets / capsules / caplets)	NULL	Unknown	Angiotensin Converting Enzyme Inhibitors	Intentional - Suspected suicide	Minor effect
	7/29/12	4724053302012	57	Male	7	9	Solid (tablets / capsules / caplets)	NULL	Unknown	Other Types of Gamma Aminobutyric Acid Anticonvulsant	Intentional - Suspected suicide	Minor effect
	7/29/12	4724053302012	57	Male	8	9	Solid (tablets / capsules / caplets)	NULL	Unknown	Tramadol	Intentional - Suspected suicide	Minor effect
	7/29/12	4724053302012	57	Male	9	9	Solid (tablets / capsules / caplets)	NULL	Unknown	Beta Blockers (Including All Propranolol Cases)	Intentional - Suspected suicide	Minor effect
7	8/6/12	10270173702012	52	Male	1	1	Solid (tablets / capsules / caplets)	1	tabs / pills / capsules	Fentanyl	Unintentional - Therapeutic error	No effect
8	8/16/12	19757193222012	16	Male	2	2	Unknown	NULL	Unknown	Fentanyl	Intentional - Abuse	Moderate effect
	8/16/12	19757193222012	16	Male	1	2	Other	1	each (e.g. bites / stings)	Buprenorphine	Intentional - Abuse	Moderate effect
9	8/30/12	24226833092012	50	Female	5	5	Solid (tablets / capsules / caplets)	NULL	Unknown	Fentanyl	Intentional - Suspected suicide	Major effect
	8/30/12	24226833092012	50	Female	1	5	Solid (tablets / capsules / caplets)	NULL	Unknown	Tapentadol	Intentional - Suspected suicide	Major effect
	8/30/12	24226833092012	50	Female	2	5	Solid (tablets / capsules / caplets)	NULL	Unknown	Morphine	Intentional - Suspected suicide	Major effect
	8/30/12	24226833092012	50	Female	3	5	Solid (tablets / capsules / caplets)	NULL	Unknown	Other Types of Antidepressant	Intentional - Suspected suicide	Major effect
	8/30/12	24226833092012	50	Female	4	5	Solid (tablets / capsules / caplets)	NULL	Unknown	Other Types of Sedative/Hypnotic/Anti-Anxiety or Anti-Psychotic Drug	Intentional - Suspected suicide	Major effect
10	9/29/12	729692973262012	17	Female	1	1	Solid (tablets / capsules / caplets)	1	tabs / pills / capsules	Fentanyl	Unintentional - General	Minor effect
11	10/23/12	23049223012012	44	Female	1	1	Patch	NULL	Unknown	Fentanyl	Intentional - Unknown	Minor effect

AAPCC Listing of Exposures to Unknown Fentanyl												
Subject	Start Date	Public Case Number	Age	Gender	Substance Rank	No of Substances	Formulation	Quantity	Quantity Unit	Major Category	Reason For Exposure	Medical Outcome
1	5/11/12	4169283642012	44	Male	1	4	Unknown	NULL	Unknown	Fentanyl	Intentional - Abuse	Death, indirect report
	5/11/12	4169283642012	44	Male	2	4	Unknown	NULL	Unknown	Methamphetamines	Intentional - Abuse	Death, indirect report
	5/11/12	4169283642012	44	Male	3	4	Solid (tablets / capsules / caplets)	NULL	Unknown	Benzodiazepines	Intentional - Abuse	Death, indirect report
	5/11/12	4169283642012	44	Male	4	4	Solid (tablets / capsules / caplets)	NULL	Unknown	Methadone	Intentional - Abuse	Death, indirect report
2	5/12/12	4170313642012	23	Female	1	3	Unknown	NULL	Unknown	Fentanyl	Intentional - Abuse	Death, indirect report
	5/12/12	4170313642012	23	Female	2	3	Solid (tablets / capsules / caplets)	NULL	Unknown	Other Types of Skeletal Muscle Relaxant	Intentional - Abuse	Death, indirect report
	5/12/12	4170313642012	23	Female	3	3	Solid (tablets / capsules / caplets)	NULL	Unknown	Benzodiazepines	Intentional - Abuse	Death, indirect report
3	5/12/12	4170373642012	42	Female	1	3	Unknown	NULL	Unknown	Fentanyl	Unknown reason	Death, indirect report
	5/12/12	4170373642012	42	Female	2	3	Solid (tablets / capsules / caplets)	NULL	Unknown	Tramadol	Unknown reason	Death, indirect report
	5/12/12	4170373642012	42	Female	3	3	Solid (tablets / capsules / caplets)	NULL	Unknown	Acetaminophen with Hydrocodone	Unknown reason	Death, indirect report
4	7/15/12	30564603582012	22	Male	1	2	Solid (tablets / capsules / caplets)	40	tabs / pills / capsules	Acetaminophen with Hydrocodone	Intentional - Abuse	Unable to follow, judged as a potentially toxic exposure
	7/15/12	30564603582012	22	Male	2	2	Powder / granules	1	each (e.g. bites / stings)	Fentanyl	Intentional - Abuse	Unable to follow, judged as a potentially toxic exposure
5	7/18/12	4264843642012	51	Female	1	5	Unknown	NULL	Unknown	Fentanyl	Intentional - Abuse	Death, indirect report
	7/18/12	4264843642012	51	Female	2	5	Solid (tablets / capsules / caplets)	NULL	Unknown	Tramadol	Intentional - Abuse	Death, indirect report
	7/18/12	4264843642012	51	Female	3	5	Liquid	NULL	Unknown	Ethanol (Beverages)	Intentional - Abuse	Death, indirect report
	7/18/12	4264843642012	51	Female	4	5	Solid (tablets / capsules / caplets)	NULL	Unknown	Benzodiazepines	Intentional - Abuse	Death, indirect report
	7/18/12	4264843642012	51	Female	5	5	Solid (tablets / capsules / caplets)	NULL	Unknown	Diphenhydramine Alone (Unknown if Over the Counter or Prescription)	Intentional - Abuse	Death, indirect report
6	8/2/12	4286983642012	36	Male	1	5	Unknown	NULL	Unknown	Fentanyl	Intentional - Abuse	Death, indirect report
	8/2/12	4286983642012	36	Male	2	5	Unknown	NULL	Unknown	Acetaminophen with Hydrocodone	Intentional - Abuse	Death, indirect report
	8/2/12	4286983642012	36	Male	3	5	Solid (tablets / capsules / caplets)	NULL	Unknown	Other Types of Skeletal Muscle Relaxant	Intentional - Abuse	Death, indirect report

AAPCC Listing of Exposures to Unknown Fentanyl												
Subject	Start Date	Public Case Number	Age	Gender	Substance Rank	No of Substances	Formulation	Quantity	Quantity Unit	Major Category	Reason For Exposure	Medical Outcome
	8/2/12	4286983642012	36	Male	4	5	Solid (tablets / capsules / caplets)	NULL	Unknown	Other Antihistamines Alone (Excluding Cough and Cold Preparations)	Intentional - Abuse	Death, indirect report
	8/2/12	4286983642012	36	Male	5	5	Solid (tablets / capsules / caplets)	NULL	Unknown	Other Types of Antidepressant	Intentional - Abuse	Death, indirect report
7	8/5/12	30611853582012	65	Male	1	3	Powder / granules	28	each (e.g. bites / stings)	Fentanyl	Intentional - Suspected suicide	Moderate effect
	8/5/12	30611853582012	65	Male	2	3	Solid (tablets / capsules / caplets)	130	tabs / pills / capsules	Methadone	Intentional - Suspected suicide	Moderate effect
	8/5/12	30611853582012	65	Male	3	3	Solid (tablets / capsules / caplets)	NULL	Unknown	Benzodiazepines	Intentional - Suspected suicide	Moderate effect
8	8/6/12	4292223642012	52	Female	1	2	Unknown	NULL	Unknown	Fentanyl	Intentional - Abuse	Death, indirect report
	8/6/12	4292223642012	52	Female	2	2	Solid (tablets / capsules / caplets)	NULL	Unknown	Diphenhydramine Alone (Unknown if Over the Counter or Prescription)	Intentional - Abuse	Death, indirect report
9	8/11/12	4299653642012	35	Female	1	4	Unknown	NULL	Unknown	Fentanyl	Intentional - Abuse	Death, indirect report
	8/11/12	4299653642012	35	Female	2	4	Solid (tablets / capsules / caplets)	NULL	Unknown	Benzodiazepines	Intentional - Abuse	Death, indirect report
	8/11/12	4299653642012	35	Female	3	4	Solid (tablets / capsules / caplets)	NULL	Unknown	Phenothiazines	Intentional - Abuse	Death, indirect report
	8/11/12	4299653642012	35	Female	4	4	Solid (tablets / capsules / caplets)	NULL	Unknown	Diphenhydramine Alone (Unknown if Over the Counter or Prescription)	Intentional - Abuse	Death, indirect report
10	10/8/12	10480443722012	43	Female	1	2	Solid (tablets / capsules / caplets)	2	tabs / pills / capsules	Oxycodone Alone or in Combination (Excluding Combination Products with Acetaminophen or Acetylsalicylic Acid)	Intentional - Abuse	Minor effect
	10/8/12	10480443722012	43	Female	2	2	Other	NULL	Unknown	Fentanyl	Intentional - Abuse	Minor effect
11	10/15/12	10491743722012	74	Male	1	1	Solid (tablets / capsules / caplets)	8	each (e.g. bites / stings)	Fentanyl	Unintentional - Therapeutic error	No effect
12	10/24/12	19960333472012	56	Female	1	2	Unknown	NULL	Unknown	Atypical Antipsychotics	Intentional - Suspected suicide	Moderate effect
	10/24/12	19960333472012	56	Female	2	2	Unknown	NULL	Unknown	Fentanyl	Intentional - Suspected suicide	Moderate effect

11.3 TRIG AERS Safety Surveillance Analysis Report

FDA AERS Safety Surveillance Analysis Report

AERS Data Release Date: 2012 Q2

Product: Transmucosal immediate-release fentanyl products (TIRF)

Sponsor: TIRF REMS Industry Group (TRIG) of Companies

Date: 14 December 2012

Status: Final

Version: 1.0

United BioSource Corporation

Table of Contents

Overview

The following Quarterly Analysis report was produced from the 2012 Q2 release of the FDA's Freedom of Information Act (FOIA) Adverse Event Reporting System (AERS) database which was made publicly available by the FDA in early October, 2012.

The AERS database comprises 3,778,243 cumulative case reports, including 181,428 new reports in the 2012 Q2 quarterly release. Of the case reports submitted in Q2 2012, forty-six (46) cases reference a transmucosal immediate-release fentanyl (TIRF) product covered by the FDA Risk Evaluation and Mitigation Strategy (REMS) for TIRF products, with an event date on or after December 28, 2011. Thirty-seven (37) of these TIRF product case reports with an event date after December 28, 2011 also specify United States as the Country of Origin and are included in the analysis results described below.

Twenty-six (26) of the 37 cases selected for analysis include at least one of the individual MedDRA Preferred Terms of Interest specified in the TRIG AERS Safety Surveillance Plan. These Preferred Terms of Interest are grouped into the following broad Categories of Interest (TRIG Categories) for aggregate reporting:

- Death
- Overdose (fatal and non-fatal)
- Misuse, abuse, addiction, and diversion
- Inappropriate
- Medication errors
- Accidental

In addition, one (1) of the 37 cases selected also specifies at least one Preferred Term from the MedDRA SMQ (Broad) *Acute Central Respiratory Depression,* which is included in this analysis as a possible symptom related to the events included in the TRIG Categories above. None of the individual Preferred Terms from this SMQ is a TRIG Preferred Term of interest; instead counts of reports listing any PT from this SMQ will be summarized into an aggregate count for the entire SMQ and reported separately.

The analysis protocol and assumptions that were used to guide this quarterly analysis are documented in the TRIG AERS Safety Surveillance Plan (*TRIG AERS Safety Surveillance Plan 14Dec2012 V3 Final.docx).* This analysis report summarizes the reporting characteristics of the AERS case reports for TIRF products covered by the FDA REMS for the TRIG companies. The results are presented in 4 sections and an additional optional section:

- **AERS Reports - Cumulative and Quarterly Summary Statistics**: this section provides summary characteristics of the reports comprising the entire AERS database which can be used to provide additional context for interpreting results of the TIRF analysis
- **TIRF Product Reports – Cumulative and Quarterly Summary Statistics**: this section

provides the summary report characteristics of case reports which were selected for the TRIG quarterly analysis, that also include a PT or SMQ of interest

- **Outcomes of Interest – Cumulative and Quarterly Summary Statistics:** this section provides counts for each individual Preferred Term of Interest, as well as for the TRIG event categories Overdose, Death, Abuse, Misuse, Inappropriate, Medication Error, Accidental, Dependence, and Drug Diversion. In addition, counts for the SMQs Drug Abuse Dependence and Withdrawal, and Acute Central Respiratory Depression are also included.
- **Signal Detection:** This section provides signal detection results for TRIG individual Preferred Terms of interest, for each TRIG event category, and for the 2 SMQ's of interest.
- **Case Details (optional upon request):** At the request of a TRIG sponsor, AERS case reports can be provided for any or all of the TIRF cases described in this report. These cases will be provided without product name/identifiers or Manufacturer ID's.

Analysis Results

AERS Reports: Quarterly and Cumulative Summary Statistics

The tables below provide a descriptive summary of the 2012 Q2AERS database. These tables include cumulative totals as well as totals for the current and prior quarter:

- Table 1: AERS Overall Case Report Counts
- Table 2, Figure 1: AERS Gender Summary
- Table 3, Figure 2: AERS Age Summary
- Table 4: AERS Report Type
- Table 5: AERS Initial and Follow up Reports
- Table 6: AERS Outcome Type
- Table 7: AERS Submission Type
- Table 8: AERS Report Source Type
- Table 9, AERS Reporter Occupation
- Table 10: AERS Country of Origin

Table 1 AERS Overall Case Report Counts[1]

Overall Database			
	Cumulative Total	Current Quarter	Prior Quarter
Reports	3,778,243	181,428	187,557

[1] From Q41997 through Q2 2012

Table 2 AERS Gender Summary

Gender			
	Cumulative Total	Current Quarter	Prior Quarter
Female	2,099,382	101,568	109,432
Male	1,359,594	62,352	64,362
Other/ Unknown	319,267	17,508	13,763
Total	3,778,243	181,428	187,557

Figure 1 AERS Gender Summary, Current and Prior Quarter

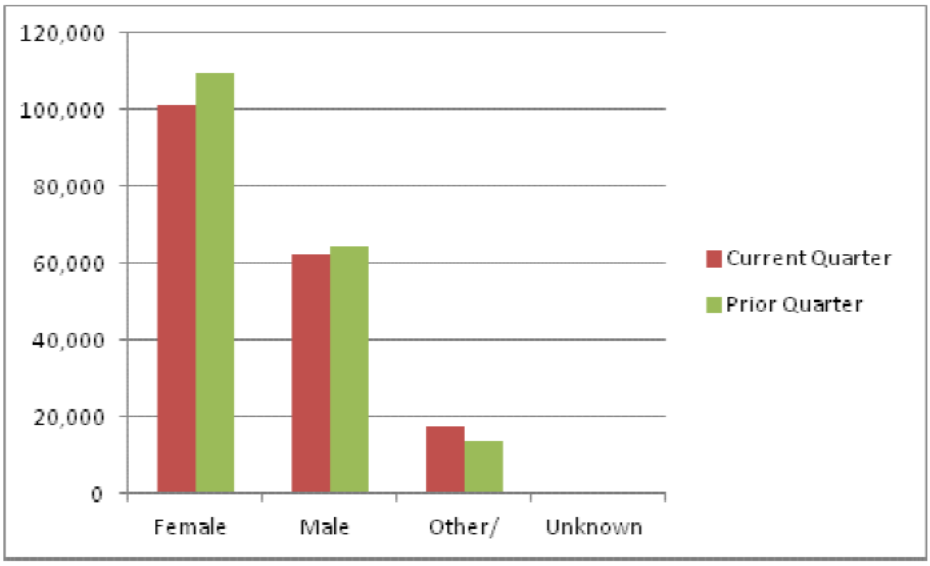

Table 3 AERS Age Summary

Age			
	Cumulative Total	Current Quarter	Prior Quarter
Age 0-2	34,306	1,223	813
Age 3-5	17,797	661	592
Age 6-10	34,726	1,583	1,070
Age 11-18	83,699	3,444	3,868
Age 19-25	116,640	5,023	6,708
Age 26-35	232,644	9,953	12,522
Age 36-64	1,203,086	57,673	63,700
Age 65+	789,151	39,277	37,526
Not Reported	1,266,194	62,591	60,758
Total	3,778,243	181,428	187,557

Figure 2 AERS Age Summary, Current and Prior Quarter

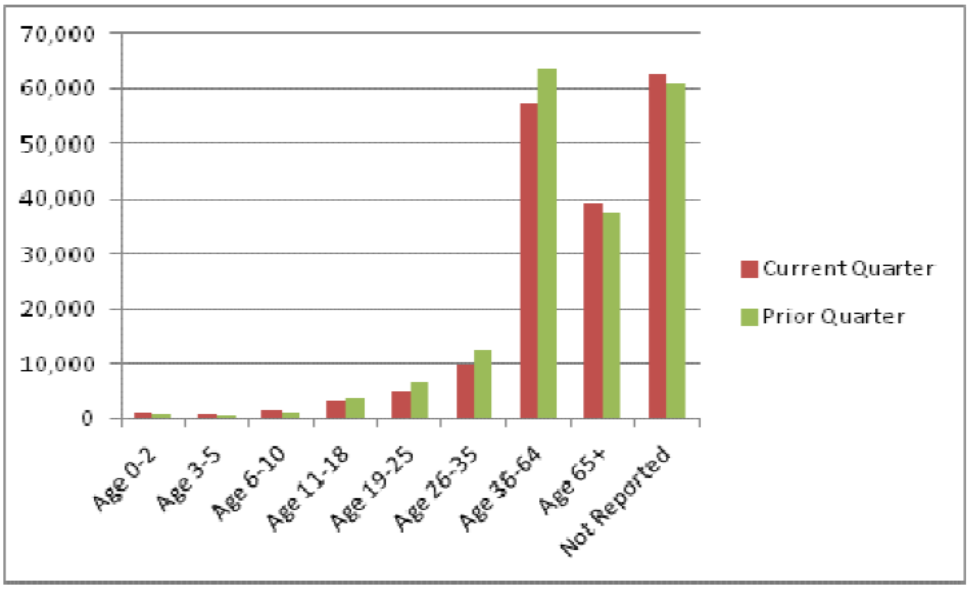

Table 4 Report Type

Report Type			
	Cumulative Total	Current Quarter	Prior Quarter
Direct	325,185	7,015	6,975
Expedited	1,951,963	106,095	105,189
Periodic	1,501,095	68,318	75,393
Total	3,778,243	181,428	187,557

Table 5 Initial / Follow-up Reports

Initial/Follow-Up			
	Cumulative Total	Current Quarter	Prior Quarter
Follow-Up	981,680	51,010	46,367
Initial	2,796,296	130,418	141,190
Unspecified	267	-	-
Total	3,778,243	181,428	187,557

Table 6 AERS Outcome Type

Outcome Type			
	Cumulative Total	Current Quarter	Prior Quarter
Congenital Anomaly	20,745	1,412	1,304
Death	413,431	19,764	22,689
Disability	131,279	7,445	4,438
Hospitalization	1,072,018	52,097	51,308
Life-Threatening	169,218	5,787	5,868
Other	1,381,924	71,097	67,804
Required Intervention	120,023	965	1,112
Total	3,308,638	158,567	154,523

Table 7 AERS Submission Type

Submission Type			
	Cumulative Total	Current Quarter	Prior Quarter
Electronic	2,011,634	158,713	162,022
Other	1,132,302	22,715	25,535
Unspecified	634,307	-	-
Total	3,778,243	181,428	187,557

Table 8 AERS Report Source Type*

Report Source Type			
	Cumulative Total	Current Quarter	Prior Quarter
Foreign	346,172	4,876	4,275
Study	99,818	1,234	925
Literature	106,909	2,745	2,962
Consumer	602,433	5,456	7,247
Health Professional	846,333	12,995	14,206
User Facility	3,715	87	64
Company Representative	142,931	1,381	2,210
Distributor	11,138	150	59
Other	283,120	5,278	4,876
Unspecified	2,320,745	164,567	166,782
Total	4,763,314	198,769	203,606

*One report may have zero, one, or multiple report sources

Table 9 AERS Reporter Occupation

Reporter Occupation			
	Cumulative Total	Current Quarter	Prior Quarter
Consumer	1,102,847	79,279	87,762
Lawyer	96,675	7,867	6,078
Other Health Professional	498,131	33,131	32,377
Pharmacist	194,271	9,187	8,065
Physician	811,278	46,401	47,072
Unspecified	1,075,041	5,583	6,203
Total	3,778,243	181,428	187,557

Table 10 AERS Country of Origin

Country of Origin			
	Cumulative Total	Current Quarter	Prior Quarter
United States	1,819,621	125,542	136,654
Unspecified	1,241,581	1,496	617
Other	717,041	54,390	50,286
Total	3,778,243	181,428	187,557

TIRF Product Reports: Quarterly and Cumulative Summary Statistics

The tables below provide descriptive analyses of AERS case reports for TIRF products that met the selection criteria as defined in the Quarterly Surveillance Plan, and also contain a TRIG Preferred Term or SMQ of interest. Results are summarized for the current quarter; prior quarter and cumulative results are included for comparison. The 2012 Q1 data release was the first AERS quarterly release covered by the REMS, however there were no cases for TIRF products that met the case selection criteria in that prior release so that information is omitted from this quarterly report.

The case selection criteria used for this analysis includes the following:

- **Brand Name:**: Case reports with specified TIRF brand names
- **Generic Fentanyl:** Case Reports referencing the generic ingredient Fentanyl, with case selection restricted to specified routes of administration and TRIG Manufacturer IDs

AERS case report selection is further restricted to only include reports for adverse events occurring on or after December 28, 2011 with United States designated as the Country of Origin. Cases with an unspecified Event Date or Country of Origin are not selected for analysis.

Of the thirty-seven (37) reports that meet all TIRF selection criteria as described above, twenty-six (26) of these reports also include a MedDRA Preferred Term of Interest for this study. In addition, one (1) report includes a MedDRA Preferred Term from the SMQ *Acute central respiratory depression SMQ*. Although the reported Preferred Term from this SMQ is not a TRIG Preferred Terms of interest, this SMQ was included as a potential symptom of the outcomes of interest and report counts are included in aggregate for this SMQ. The twenty seven (27) reports that reference a PT or SMQ of interest are further characterized in this section of the report.

A majority of the reports are for female patients, aged 36 to 64. Consumer is the most commonly reported Occupation, reported on nearly 74% (20 of 27) of the reports. Additionally, on 81% (22 of 27) of the reports, the TIRF product is reported as the primary suspect drug. Characteristics of these 27 reports are further described in the tables below:

Table 11 Patient Counts for TIRF case reports containing Events of Interest

Patient Counts	2012 Q2	Total to Date
All Reports for TIRF Drugs with event date after 12/28/2012	46	46
US Reports Only	37	37
Reports meeting TRIG selection criteria and containing MedDRA Term of Interest	26	26
Reports meeting TRIG selection criteria and matching Acute Central Respiratory Depression SMQ	1	1

Table 12 Gender Summary for TIRF case reports containing Events of Interest

Gender	2012 Q2	Total to Date
Males	6	6
Females	20	20
Unknown	1	1

Table 13 Age Summary for TIRF case reports containing Events of Interest

Age	2012 Q2	Total to Date
Age 0-2	0	0
Age 3-5	0	0
Age 6-10	0	0
Age 11-18	0	0
Age 19-25	0	0
Age 26-35	1	1
Age 36-64	16	16
Age 65+	3	3
Unknown Age	7	7

.Table 14 Reported outcomes for TIRF case reports containing Events of Interest*

Outcome	2012 Q2	Total to Date
Congenital Anomaly	0	0
Death	1	1
Disability	0	0
Hospitalization	4	4
Life Threatening	0	0
Requires Intervention	0	0
Other	9	9
Not Specified	13	13

*Cases may have 0, 1 or multiple outcomes specified

Table 15 Submission type for case reports referencing TIRF products

Submission Type	2012 Q2	Total to Date
Electronic	27	27
Other	0	0
Unspecified	0	0

Table 16 Report source for TIRF case reports containing Events of Interest

Report Source	2012 Q2	Total to Date
Foreign	0	0
Study	0	0
Literature	0	0
Consumer	0	0
Health Professional	0	0
User Facility	0	0
Company Representative	0	0
Distributor	0	0
Other	0	0
Unspecified	27	27

Table 17 Reporter occupation for TIRF case reports containing Events of Interest

Reporter Occupation	2012 Q2	Total to Date
Consumer	20	20
Lawyer	0	0
Other Health Professional	5	5
Pharmacist	0	0
Physician	1	1
Unspecified	1	1

Table 18 Role code for TIRF products

Role Code	2012 Q2	Total to Date
Primary Suspect	22	22
Concomitant	5	5

Table 19 Report Type for TIRF case reports containing Events of Interest

Report Type	2012 Q2	Total to Date
Expedited	9	9
Periodic	18	19

Outcomes of Interest - Cumulative and Quarterly Summary Statistics

The following tables summarize the TRIG Preferred Terms of Interest that were reported on the case reports for TIRF products that met the selection criteria for this analysis.

Each case report may include one or more Preferred Terms. A total of 36 Preferred Terms of Interest for this study are reported across 26 case reports selected for TIRF products that contain at least 1 TRIG Preferred Term of Interest. The most commonly reported Term is "Off label use" (18) followed by "Drug prescribing error" (7). In addition, one (1) Case report includes a term from the SMQ *Acute central respiratory depression.* The tables below summarize the reported terms:

- Table 20: Count of reported TRIG Preferred Terms of interest
- Table 21: Count of reported Preferred Terms by TRIG Category

Table 20 Count of reported TRIG Preferred Terms of Interest

Unique Preferred Term	2012 Q2		Total to Date	
	N	%	N	%
Brand Name Analysis				
Accidental death	0	0.0%	0	0.0%
Accidental drug intake by child	0	0.0%	0	0.0%
Accidental exposure	0	0.0%	0	0.0%
Accidental overdose	0	0.0%	0	0.0%
Accidental poisoning	0	0.0%	0	0.0%
Agonal death struggle	0	0.0%	0	0.0%
Apparent death	0	0.0%	0	0.0%
Brain death	0	0.0%	0	0.0%
Cardiac arrest	0	0.0%	0	0.0%
Cardiac death	0	0.0%	0	0.0%
Cardio-respiratory arrest	0	0.0%	0	0.0%
Counterfeit drug administered	0	0.0%	0	0.0%
Death	0	0.0%	0	0.0%
Death neonatal	0	0.0%	0	0.0%
Death of companion	0	0.0%	0	0.0%
Death of relative	0	0.0%	0	0.0%
Dependence	0	0.0%	0	0.0%
Drug abuse	0	0.0%	0	0.0%
Drug abuser	0	0.0%	0	0.0%
Drug administered at inappropriate site	0	0.0%	0	0.0%
Drug administered to patient of inappropriate age	0	0.0%	0	0.0%
Drug administration error	1	2.8%	1	2.8%
Drug dependence	0	0.0%	0	0.0%
Drug dependence, antepartum	0	0.0%	0	0.0%
Drug dependence, postpartum	0	0.0%	0	0.0%
Drug dispensing error	1	2.8%	1	2.8%
Drug diversion	0	0.0%	0	0.0%
Drug dose omission	1	2. 8%	1	2. 8%
Drug label confusion	0	0.0%	0	0.0%

Drug name confusion	0	0.0%	0	0.0%
Drug prescribing error	7	19. 4%	8	19. 4%
Drug Withdrawal Syndrome	3	8.3%	3	8.3%
Ex-drug abuser	0	0.0%	0	0.0%
Expired drug administered	1	2. 8%	1	2.8%
Inappropriate schedule of drug administration	0	0.0%	0	0.0%
Incorrect dose administered	0	0.0%	0	0.0%
Incorrect drug administration duration	0	0.0%	0	0.0%
Incorrect drug administration rate	0	0.0%	0	0.0%
Incorrect drug dosage form administered	0	0.0%	0	0.0%
Incorrect route of drug administration	0	0.0%	0	0.0%
Incorrect storage of drug	0	0.0%	0	0.0%
Intentional drug misuse	0	0.0%	0	0.0%
Intentional overdose	0	0.0%	0	0.0%
Intercepted drug dispensing error	0	0.0%	0	0.0%
Intercepted drug prescribing error	0	0.0%	0	0.0%
Intercepted medication error	0	0.0%	0	0.0%
Labelled drug-disease interaction medication error	0	0.0%	0	0.0%
Labelled drug-drug interaction medication error	0	0.0%	0	0.0%
Medication error	0	0.0%	0	0.0%
Medication overuse headache	0	0.0%	0	0.0%
Multiple drug overdose	0	0.0%	0	0.0%
Multiple drug overdose accidental	0	0.0%	0	0.0%
Multiple drug overdose intentional	0	0.0%	0	0.0%
Multiple use of single-use product	0	0.0%	0	0.0%
Off label use	18	50.0%	18	50.%
Overdose	0	0.0%	0	0.0%
Polysubstance dependence	0	0.0%	0	0.0%
Poor quality drug administered	0	0.0%	0	0.0%
Respiratory arrest	0	0.0%	0	0.0%
Substance abuse	0	0.0%	0	0.0%
Substance abuser	0	0.0%	0	0.0%
Substance-induced mood disorder	0	0.0%	0	0.0%
Substance-induced psychotic disorder	0	0.0%	0	0.0%
Sudden cardiac death	0	0.0%	0	0.0%
Sudden death	0	0.0%	0	0.0%
Sudden unexplained death in epilepsy	0	0.0%	0	0.0%
Therapy naive	0	0.0%	0	0.0%
Toxicity to various agents	0	0.0%	0	0.0%
Underdose	0	0.0%	0	0.0%
Withdrawal syndrome	3	8.3	3	8.3%
Wrong drug administered	0	0.0%	0	0.0%
Wrong technique in drug usage process	1	2. 8%	1	2. 8%
Total Number of Preferred Terms Reported	**36**	**100%**	**36**	**100%**

Table 21 Count of reported Events of Interest grouped by TRIG Category

Events by Category	Q2 2012		Total to Date	
	N	%	N	%
Overdose	**0**	0.0%	**0**	0.0%
Accidental overdose	0	0.0%		
Intentional overdose	0	0.0%		
Multiple drug overdose	0	0.0%		
Multiple drug overdose accidental	0	0.0%		
Multiple drug overdose intentional	0	0.0%		
Overdose	0	0.0%		
Death	**0**	0.0%	**0**	0.0%
Accidental death	0	0.0%		
Agonal death struggle	0	0.0%		
Apparent death	0	0.0%		
Brain death	0	0.0%		
Cardiac arrest	0	0.0%		
Cardiac death	0	0.0%		
Cardio-respiratory arrest	0	0.0%		
Death	0	0.0%		
Death neonatal	0	0.0%		
Death of companion	0	0.0%		
Death of relative	0	0.0%		
Respiratory arrest	0	0.0%		
Sudden cardiac death	0	0.0%		
Sudden death	0	0.0%		
Sudden unexplained death in epilepsy	0	0.0%		
Misuse	0	0.0%	**0**	0.0%
Intentional Drug Misuse	0	0.0%		
Medication overuse headache	0	0.0%		
Drug abuse dependence and withdrawal SMQ	*6*	*N/A*		
Abuse	0	0.0%	**0**	0.0%
Drug abuse	0	0.0%		
Drug abuser	0	0.0%		
Ex-drug abuser	0	0.0%		
Substance abuse	0	0.0%		
Substance abuser	0	0.0%		
Substance-induced mood disorder	0	0.0%		
Substance-induced psychotic disorder	0	0.0%		
Drug abuse dependence and withdrawal SMQ	*6*	*N/A*		
Inappropriate	18	50.0%	18	50.0%
Drug administered at inappropriate site	0	0.00%		
Drug administered to patient of inappropriate age	0	0.00%		
Inappropriate schedule of drug administration	0	0.00%		
Off label use	18	50.0%		
Medication Error	12	33.3%	12	33.3%
Accidental drug intake by child	0	0.0%		
Counterfeit drug administered	0	0.0%		
Drug administered to patient of inappropriate age	0	0.0%		

Drug administration error	1	2.8%		
Drug dispensing error	1	2.8%		
Drug dose omission	1	2.8%		
Drug label confusion	0	0.0%		
Drug name confusion	0	0.0%		
Drug prescribing error	7	19.4%		
Expired drug administered	1	2. 8%		
Inappropriate schedule of drug administration	0	0.0%		
Incorrect dose administered	0	0.0%		
Incorrect drug administration duration	0	0.0%		
Incorrect drug administration rate	0	0.0%		
Incorrect drug dosage form administered	0	0.0%		
Incorrect route of drug administration	0	0.0%		
Incorrect storage of drug	0	0.0%		
Intercepted drug dispensing error	0	0.0%		
Intercepted drug prescribing error	0	0.0%		
Intercepted medication error	0	0.0%		
Labelled drug-disease interaction medication error	0	0.0%		
Labelled drug-drug interaction medication error	0	0.0%		
Medication error	0	0.0%		
Multiple use of single-use product	0	0.0%		
Poor quality drug administered	0	0.0%		
Therapy naïve	0	0.0%		
Underdose	0	0.0%		
Wrong drug administered	0	0.0%		
Wrong technique in drug usage process	1	2.8%		
Accidental	0	0.0%	**0**	0.0%
Accidental drug intake by child	0	0.0%		
Accidental exposure	0	0.0%		
Accidental overdose	0	0.0%		
Accidental poisoning	0	0.0%		
Multiple drug overdose accidental	0	0.0%		
Toxicity to various agents	0	0.0%		
Dependence	6	16.7%	6	14.3%
Dependence	0	0.0%		
Drug dependence	0	0.0%		
Drug dependence, antepartum	0	0.0%		
Drug dependence, postpartum	0	0.0%		
Drug Withdrawal Syndrome	3	8.3%		
Polysubstance dependence	0	0.0%		
Withdrawal syndrome	3	8.3%		
Drug Diversion	18	50.0%	18	50.0%
Drug diversion	0	0.0%		
Off label use	18	50%		
Respiratory Depression	1	N/A	1	N/A
Acute central respiratory depression SMQ	*1*	*N/A*		

Signals of Disproportionate Reporting

Data mining signal detection was carried out for the 37 TIRF cases selected by TRIG case selection criteria, using the AERS database as the background. In a data mining analysis using a spontaneous reporting database such as AERS, a traditional "denominator" (e.g. the number of patients exposed to a particular drug and/or how long they've been exposed) is not known. To overcome this limitation, data mining methods produce a ratio of disproportionate reporting, comparing the number of reports for a particular Drug / Adverse Event (AE) combination to the number of reports for that AE across all of the other drugs in the AERS database. A disporportionality ratio of 1 indicates that that the AE is being reported for the drug of interest at the same rate as it is being reported for all other drugs in the background; a ratio of 2 means that it is being reported at twice the background rate.

There are several commonly used algorithms that produce disproportionality statistics. Three of the most common algorithms were utilized in this analysis. Each of these algorithms also includes a measure of confidence:

- Proportional Reporting Ratio (PRR), Chi Square
- Reporting Ratio (RR), Statistical Unexpectedness (1/P)
- Multi-gamma poisson shrinker (MGPS), lower bounds of the 95% confidence interval (EB05)

There is no single international standard for signal detection thresholds based on AERS and other spontaneous report databases. The CIOMS VIII Working Group (CIOMS Geneva 2010) dedicates a chapter (VII) to "more complex quantitative signal detection methods", and provides thoughtful perspectives on the role of statistical analysis in the setting of pharmacovigilance. Despite a lack of standards, signaling is commonly defined by the following thresholds:

- PRR: PRR>2, Chi Square >4, and number of reports>3 – considered to be more sensitive but not as specific
- MGPS: EB05>2 (lower bounds of the 95% confidence interval of EBGM) – considered to be more specific, but not as sensitive.
- RR: RR>1, Statistical Unexpectedness (1/P-value) >system calculated, Bonferroni corrected threshold – considered to have intermediate sensitivity / specificity[1]

A Drug / AE combination that crosses a data mining signal threshold is not necessarily indicative that the drug is the cause of that adverse event. For instance, many adverse events that produce high disproportionality scores are related to the reported drug's indication. Therefore, disproportionality results should be interpreted in the context of other information known about the drug.

[1] Hochberg AM, Hauben M, Pearson RK, O'Hara DJ, Reisinger SJ, Goldsmith DI, Gould AL, Madigan D., An evaluation of three signal-detection algorithms using a highly inclusive reference event database. Drug Saf. 2009;32(6):509-25. doi: 10.2165/00002018-200932060-00007.

Only terms that cross the signaling threshold for at least one of the three data mining algorithms utilized for the analysis are included in the tables below (note that MGPS scores are only calculated when the total number of case reports for the drug and the total number of case reports for the adverse event both exceed one hundred (100), so these scores are not included in the tables below for this quarter). The following tables describe the results of data mining signal detection carried out for the TIRF cases of interest, using the AERS database as the background:

- Table 22 Signals of Disproportionate Reporting, Preferred Terms of Interest
- Table 23 Signals of Disproportionate Reporting, TRIG Categories of Interest
- Table 24 Signals of Disproportionate Reporting, SMQs of Interest

Table 22 Signals of Disproportionate Reporting, Preferred Terms of Interest

AdverseEvent	Reports with Drug & Event	Reports with Event	Reporting Ratio	Statistical Unexpectedness	PRR	Chi Square
Brand Name Analysis						
Off label use	18	12,535	146.63	34.41	146.84	2468.16
Drug prescribing error	7	3,367	212.30	14.35	212.74	1269.54
Withdrawal syndrome	3	5,510	55.60	4.63	55.63	111.05

Table 23 Signals of Disproportionate Reporting, TRIG Categories of Interest

AdverseEvent	Reports with Drug & Event	Reports with Event	Reporting Ratio	Statistical Unexpectedness	PRR	Chi Square
Inappropriate	18	21,189	86.75	30.32	86.82	1449.24
Diversion	18	12,944	141.45	34.13	141.65	2380.03
Medication Error	12	130,192	9.41	8.63	9.41	84.93
Dependence	6	42,746	14.33	5.44	14.34	62.39

Table 24 Signals of Disproportionate Reporting, SMQ's of Interest

AdverseEvent	Reports with Drug & Event	Reports with Event	Reporting Ratio	Statistical Unexpectedness	PRR	Chi Square
Drug abuse, dependence and withdrawal	6	173846	3.52	2.19	3.52	8.88

Not surprisingly, relatively robust signals were generated for the Preferred Terms of Interest: "Off label Use" and "Drug prescribing error". A weaker signal was generated for the Preferred Term of Interest "Drug withdrawal syndrome". These are known adverse events for TRIG products, and are the subject of the TIRF REMS program. When analyzed according to TRIG Categories of Interest, relatively robust signals were also generated for "Inappropriate use", "Drug diversion", "Medication error", and "Drug dependence". When examined by MedDRA SMQ, the SMQ "Drug abuse, dependence and withdrawal" generated a somewhat weak signal of disproportionate reporting.

Data mining results for these adverse events will continue to be monitored over time to understand the impact of the REMS program on the overall reporting rates for these events of interest.

Patient Case Listing

Case Details (optional upon request): At the request of a TRIG sponsor, AERS case reports can be provided for any or all of the TIRF cases described in this report. These cases will be provided without product name/identifiers or Manufacturer ID's.

11.4 Periodic Stakeholder Surveys

11.4.1 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	Final Wave 1, Version 1.0
Product Name:	Transmucosal Immediate Release Fentanyl
Sponsor:	**TIRF REMS Industry Group (TRIG) of Companies:** Archimedes Pharma US Inc. Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Insys Therapeutics Meda Pharmaceuticals Mallinckrodt (the Pharmaceuticals Business of Covidien) Par Pharmaceutical, Inc. ProStrakan, Inc.
Date:	14 December 2012

Confidentiality Statement

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LIST OF ABBREVIATIONS

CI	Confidence Interval
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HCP	Healthcare Professional
KAB	Knowledge, Attitudes and Behavior
PPAF	Patient-Prescriber Agreement Form
REMS	Risk Evaluation and Mitigation Strategy
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
SAP	Statistical Analysis Plan
SERP	Safety Event Report Planning
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 Archimedes Pharma United States (US) Inc., Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.), Insys Therapeutics, Meda Pharmaceuticals, Mallinckrodt (a Pharmaceuticals Business of Covidien), Par Pharmaceutical, Inc., and ProStrakan, Inc. At the time of protocol development for the Knowledge, Attitude, and Behavior (KAB) surveys, Sandoz was also a member of the TRIG; however, Sandoz terminated their involvement in the TIRF REMS Access program, effective 15 September 2012.

The Food and Drug Administration (FDA) has determined that a class-wide 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 bythe 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' and caregivers' knowledge, attitudes, and behavior (KAB) regarding the safe use of TIRF medicines as described in the educational materials. The protocol describes 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 or educational materials to make them more effective in achieving the goals of the REMS.

Results from the surveys will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

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, which can be found in Appendix A.

3.1 Survey Sample

This survey was conducted among patients who had a prescription filled for a TIRF medicine within the 90 days prior 12 September 2012. A target sample of 300 patients treated with TIRF medicines were to be surveyed in this first KAB survey conducted from 24 September 2012 to 30 October 2012. Subject recruitment was performed via a direct letter

program, and some subjects were also invited through a national pharmacy chain network partner.

Patients 18 years of age or older and caregivers 18 years of age or older who cared for patients unable to take the survey for themselves were eligible to participate in the survey. Respondents or their 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 in this survey.

Respondents who participated in the first wave of the TIRF survey will not be eligible to participate in subsequent survey waves.

Potential participants were recruited via a letter of invitation sent through the United States Postal Service (USPS). The required number of completed surveys was not achieved; therefore, a second mailing was sent to non-respondents through USPS mail with subsequent follow-up to maximize participation. In the second mailing, reminder letters were sent to those patients who had not yet responded. In the third mailing, invitations were sent out to patients not included in the original mailing.

Patients were given the option of taking the survey by telephone via the Survey Coordinating Center or online via a secure website. All participating patients were offered a $25 gift card 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 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 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**
12d	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
	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 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:		
10	TIRF medicines should only be taken by patients who are opioid tolerant.	***True***
11a	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***
Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
12b	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 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**
Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.		
11b	If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.	***True***
Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
12c	TIRF medicines should be taken exactly as prescribed by the doctor.	***True***
16b	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**
Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.		
11c	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 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**
Please answer True, False, or I don't know for each of the following statements.		
11d	A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	***False***
Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
16a	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 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**
Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
12a	TIRF medicines should be stored in a safe place out of the reach of children.	***True***
16c	TIRF medicines must be disposed of as described in the specific product's Medication Guide.	***True***
16e	A TIRF medicine can cause an overdose and death in any child who takes it.	***True***
13	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

According to the prospective Statistical Analysis Plan (SAP, 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 3 months) ***or Yes*** to Question 3 (Caregiver for someone who had filled a prescription for a TIRF medicine in the last 3 months), ***No*** to Question 4 (participated in past survey; not applicable for Wave 1), ***selected an age group >18 years of age*** for Question 5 (patient and caregiver), and ***No*** to Question 7 (worked for a TRIG company, UBC, or FDA).

A completed survey was a survey in which all non-eligibility questions as appropriate were answered. Note that some questions may not been answered because of skip logic in the survey questionnaire.

4.1.2 Sub-populations of Interest

The following subgroup analyses were conducted if the subgroup included at least 20 respondents.

- Sub-population S-1: Reading Medication Guide (Question 17, 22, and 23) (***Patients who received the Medication Guide and read at least most of it or Patients 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-population analysis S-2: Understanding of Medication Guide (Question 24) ***(Respondents who understood all of it or most of it, Respondents who understood some of it, Respondents who answered None or "I don't know", Respondents who answered "I don't know" to receipt or reading of the Medication Guide.)***

- Sub-population S-3: Time to complete survey-Internet (***<10 min, 10 to <20 min, or ≥20 min***);
- Sub-population S-4: Time to complete survey-Telephone (***<10 min, 10 to <20 min, or ≥20 min***);
- Sub-population S-5: Modality to complete survey (***Internet or telephone***)
- Sub-population S-6: Highest level of education (Question 36) (***less than, some, or High School graduate/GED, or prefer not to answer, Some college or associated degree, Bachelor's degree or Master's degree, or Professional or Doctoral degree)***
- Sub-population S-7: Age group of respondents (Question 5) (***18 to 39, 40 to 49, 50 to 59, 60 or older)***

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 responses 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 3.2).

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.

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

A patient may have reported an adverse event or other safety event while taking a TIRF product either in free text fields in the survey or while in conversation with the Survey Coordinating Center. If the event was mentioned to a Survey Coordinating Center Associate, the Associate documented the safety event and the respondent's contact information. The respondent was also informed that a representative from the appropriate TIRF medicine manufacturer might contact them to obtain additional information about the safety event. The Internet surveys were monitored for any comments recorded in the free text fields. Information on all reports (Internet or phone) that constituted an adverse event or other safety event was forwarded to the appropriate TIRF medicine manufacturer for processing within 1 business day of awareness of the event as outlined in the Safety Event Reporting Plan (SERP).

5. RESULTS

Results of the patient responses to questions in the KAB survey are summarized in this section.

5.1 Survey Participants

5.1.1 Survey Participant Administration Results

Based on the number of prescriptions filled during the 90 days prior to 12 September 2012, the national pharmacy chain network partner identified 1112 possible participants among patients and caregivers. All of these possible participants were sent a survey invitation letter. A total of 899 follow up letters were sent to non-responders on 08 October 2012. Of the 1112 possible participants, 198 respondents indicated interest in the survey and were screened for eligibility to participate and 192 respondents met eligibility criteria and completed the survey (Table 1). Of these 192 respondents, 112 (56.6%) completed the survey online, and 80 (40.4%) completed it by telephone.

Although, the survey had a target of 300 eligible completed responders, the initial population of 1112 possible participants was small. The response of 192 completed surveys is within the

expected response rate (10%) to mailed invitations. To increase participation in the survey, recruitment methodology and inclusion criteria will be evaluated in future survey waves.

Table 1. Survey Participant Administration Results

Summary Statistic	Screened Patients/Caregivers N=198[1]	
	All Respondents	
	N	%
Number of invitations issued to patients/caregivers	1112	
Number of reminder letters issued to patients/caregivers	899	
Number of patients/caregivers screened for participation	198[1]	
Number of patients/caregivers eligible for participation	192	
Number of patients/caregivers completing the survey	192	97.0
By telephone	80	40.4
By internet	112	56.6

[1] This is the denominator for the percentages in this table (N=198).

Of the 198 respondents, the screening procedure identified 192 eligible participants (including 190 patients and 2 caregivers) all of whom completed the survey (Table 2). Due to the small number of caregivers participating in the survey, the majority of results are reported for patients and caregivers combined.

Table 2. Survey Participant Screening Results

Question	All Respondents N=198		Eligible and Complete Respondents N=192	
	N	%	N	%
5.2 Question 1: Do you agree to participate in this survey?				
Yes	197	99.5	192	100.0
No[1]	1	0.5		
Question 2: Within the last 3 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	191	96.5	190	99.0
No[1]	5	2.5	2	1.0
I don't know	1	0.5		
Question not asked[2]	1	0.5		
Question 3: Are you a caregiver for someone who has filled a prescription for a TIRF medicine within the last 3 months? As a reminder, TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of any of these brands.				
Yes	2	1.0	2	1.0
No[1]	4	2.0		
I don't know[1]	0	0.0		
Question not asked [2]	192	97.0	190	99.0

(continued)

Table 2. Survey Participant Screening Results

Question	All Respondents N=198		Eligible and Complete Respondents N=192	
	N	%	N	%
Question 4: Have you ever taken part in a survey about a TIRF medicine before?				
Yes	2	1.0	2	1.0
No	185	93.4	184	95.8
I don't know	6	3.0	6	3.1
Question not asked [2]	5	2.5		
Question 5: Which of the following groups best describes your age?				
Under 18[1]	0	0.0		
18 – 29	6	3.0	6	3.1
30 – 39	17	8.6	17	8.9
40 – 49	49	24.7	49	25.5
50 – 59	73	36.9	72	37.5
60 – 69	40	20.2	40	20.8
70 or older	8	4.0	8	4.2
Prefer not to answer[1]	0	0.0		
Question not asked[2]	5	2.5		
Question 6: Which of the following groups best describes the patient's age? (Caregivers, only)				
Under 16	0	0.0		
16 – 29	0	0.0		
30 – 39	0	0.0		
40 – 49	0	0.0		
50 – 59	0	0.0		
60 – 69	2	1.0	2	1.0
70 or older	0	0.0		
Prefer not to answer	0	0.0		
Question not asked[2]	196	99.0	190	99.0

(continued)

Table 2. Survey Participant Screening Results

Question	All Respondents N=198		Eligible and Complete Respondents N=192	
	N	%	N	%
Question 7: 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		
Archimedes Pharma US Inc.[1]	0	0.0		
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)[1]	0	0.0		
Endo Pharmaceuticals Inc.[1]	0	0.0		
Insys Therapeutics[1]	0	0.0		
Mallinckrodt (a Pharmaceuticals Business of Covidien)[1]	1	0.5		
Meda Pharmaceuticals[1]	0	0.0		
Par Pharmaceutical, Inc.[1]	0	0.0		
ProStrakan, Inc.[1]	0	0.0		
Sandoz Inc.[1]	0	0.0		
Teva Pharmaceuticals, Ltd.[1]	0	0.0		
United BioSource Corporation[1]	0	0.0		
McKesson Specialty Care Solutions[1]	0	0.0		
RelayHealth[1]	0	0.0		
FDA[1]	0	0.0		
No[4]	192	97.0	192	100.0
I don't know[1]	0	0.0		
Question not asked[2]	5	2.5		

1 Ineligible to participate in the survey.

2 Question not asked due to a previous question elimination

3 More than 1 response can be selected, so percentages may not sum to 100%

4 Ineligible if selected in addition to another response

Of the 192 patient/caregivers, 112 (56.6%) completed the survey online, and 80 (40.4%) completed it by telephone (Table 3). Those taking the survey online took an average of 17.5 minutes to complete it, while those taking it by telephone took an average of 13.7 minutes.

Table 3. Time to Complete Survey

Time to Complete Survey for Completers (Minutes)			
Summary Statistic	**Telephone**	**Internet**	**Total[1]**
N	80	112	192
Mean (Standard Deviation)	17.5 (4.69)	13.7 (6.86)	15.3 (6.32)
Minimum	10	5	5
Median	16.5	11.6	14.9
Maximum	38	42	42
Category			
0 – <5 Minutes	0	0	0
5 – <10 Minutes	1	37	38
10 – <15 Minutes	21	40	61
15 – <20 Minutes	40	21	61
20 – <25 Minutes	13	6	19
25 – <30 Minutes	2	4	6
30 Minutes or More	3	4	7

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

5.2.1 Patient/Caregiver Demographics

The demographic characteristics of respondents are shown in Table 4. The majority of respondents were above the age of 40 years (88.0%), female (63.0%), and had at least some college or Associate's degree or higher education(153, 79.7%). Participants were largely from the Midwest (32.3%) or South (39.6%) with the Northeast accounting for 13.5% and the West 14.0% of the respondents.

Table 4. Demographic Characteristics of Eligible Patients/Caregivers

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[1]	
	n	%	n	%	n	%
Question 5: Which of the following groups best describes your age?						
18 – 29	6	3.2	0	0	6	3.1
30 – 39	16	8.4	1	50.0	17	8.9
40 – 49	49	25.8	0	0	49	25.5
50 – 59	72	37.9	0	0	72	37.5
60 – 69	39	20.5	1	50.0	40	20.8
70 or older	8	4.2	0	0	8	4.2
Question 35: What is your gender?						
Male	70	36.8	1	50.0	71	37.0
Female	120	63.2	1	50.0	121	63.0
Prefer not to answer	0	0	0	0	0	0.0
Question 36: What is the highest level of education you have completed?						
Less than high school	2	1.1	0	0	2	1.0
Some high school	2	1.1	0	0	2	1.0
High School graduate/GED	34	17.9	0	0	34	17.7
Some college/Associate's degree	80	42.1	0	0	80	41.7
Bachelor's degree	37	19.5	1	50.0	38	19.8
Master's degree	27	14.2	1	50.0	28	14.6
Professional or Doctoral degree	7	3.7	0	0	7	3.6
Prefer not to answer	1	0.5	0	0	1	0.5

(continued)

Table 4. Demographic Characteristics of Eligible Patients/Caregivers

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[1]	
	n	%	n	%	n	%
Question 37: What is the main language you speak at home? (Please select only one.)						
English	189	99.5	2	100.0	191	99.5
French	0	0	0	0	0	0.0
Spanish	0	0	0	0	0	0.0
Portuguese	0	0	0	0	0	0.0
Italian	0	0	0	0	0	0.0
German	0	0	0	0	0	0.0
Chinese	0	0	0	0	0	0.0
Japanese	0	0	0	0	0	0.0
Korean	0	0	0	0	0	0.0
Other	0	0	0	0	0	0.0
Prefer not to answer	1	0.5	0	0	1	0.5
Question 38: Are you Hispanic or Latino?						
Yes	4	2.1	0	0	4	2.1
No	186	97.9	2	100.0	188	97.9
Prefer not to answer	0	0	0	0	0	0.0
Question 38: For informational purposes only, indicate which of the following U.S. census categories best describes your race?						
American Indian or Alaska Native	5	2.6	0	0	5	2.6
Asian (origins of Far East, Southeast Asia or the Indian subcontinent)	1	0.5	0	0	1	0.5
Black or African American	8	4.2	0	0	8	4.2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0.0
White	170	89.5	2	100.0	172	89.6
Other	4	2.1	0	0	4	2.1
Prefer not to answer	2	1.1	0	0	2	1.0

(continued)

Table 4. Demographic Characteristics of Eligible Patients/Caregivers

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[1]	
	n	%	n	%	n	%
Geographic Distribution (based on Question 40 – State or US Territory)[2]						
Northeast	26	13.7	0	0.0	26	13.5
Midwest	62	32.6	0	0.0	62	32.3
South	74	38.9	2	100.0	76	39.6
West	28	14.7	0	0.0	28	14.6
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] 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.

5.2.2 TIRF Medicines Educational 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 9).

Most respondents (173, 90.1%), reported they had received a Medication Guide for the TIRF medicine prescribed to them. Of these 173 respondents, 158 (91.3%) received the Medication Guide from the pharmacy; 167 (96.5%) read the Medication Guide; of those who read it, 109 (65.3%) read all of it and 41 (24.6%) read most of it. From these 167 respondents, 96 (57.5%) reported that they understood all of the Medication Guide and 58 (34.7%) reported that they understood most of it. There were 104 (60.1%) of the 173 respondents who indicated that someone had offered to explain the Medication Guide to them.

Table 5. Responses to Questions About TIRF Medication Guides

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[1]	
	n	%	n	%	n	%
Question 17: Have you / you or the patient ever received a Medication Guide for the TIRF medicine that was prescribed for you/the patient?						
Yes	172	90.5	1	50.0	173	90.1
No	7	3.7	1	50.0	8	4.2
I don't know	11	5.8	0	0.0	11	5.7
Question 18: Did you receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?[2]						
Yes	86	50.0	0	0.0	86	49.7
No	75	43.6	1	100.0	76	43.9
I don't know	11	6.4	0	0.0	11	6.4
N/A (answered ***No*** or ***I don't know*** to Question 17)	18		1		19	
Question 19: When was the Medication Guide given to you?[2]						
At the first appointment with the doctor who prescribed the TIRF medicine	59	68.6	0	0.0	59	68.6
At the last appointment with the doctor who prescribed the TIRF medicine	3	3.5	0	0.0	3	3.5
I don't remember	24	27.9	0	0.0	24	27.9
N/A (answered ***No*** or ***I don't know*** to Question 17 or ***No*** or ***I don't know*** to Question 18)	104		2		106	
Question 20: Did you receive the Medication Guide from the pharmacy?[2]						
Yes	157	91.3	1	100.0	158	91.3
No	11	6.4	0	0.0	11	6.4
I don't know	4	2.3	0	0.0	4	2.3
N/A (answered ***No*** or ***I don't know*** to Question 17)	18		1		19	

(continued)

Table 5. Responses to Questions About TIRF Medication Guides

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[1]	
	n	%	n	%	n	%
Question 21: When was the most recent time that you received a Medication Guide for the TIRF medicine at the pharmacy? [2]						
Only with the first filled prescription	5	3.2	1	100.0	6	3.8
Each time a prescription is filled	139	88.5	0	0.0	139	88.0
Other[3]	7	4.5	0	0.0	7	4.4
I don't know	6	3.8	0	0.0	6	3.8
N/A (answered ***No*** or ***I don't know*** to Question 17 or ***No*** or ***I don't know*** to Question 20)	33		1		34	
Question 22: Did you read the Medication Guide? [2]						
Yes	166	96.5	1	100.0	167	96.5
No	6	3.5	0	0.0	6	3.5
I don't know	0	0.0	0	0.0	0	0.0
N/A (answered ***No*** or ***I don't know*** to Question 17)	18		1		19	
Question 23: How much did you read? [2]						
All of it	109	65.7	0	0.0	109	65.3
Most of it	40	24.1	1	100.0	41	24.6
Some of it	17	10.2	0	0.0	17	10.2
I don't know	0	0.0	0	0.0	0	0.0
N/A (answered ***No*** or ***I don't know*** to Question 17 or ***No*** or ***I don't know*** to Question 22)	24		1		25	

(continued)

Table 5. Responses to Questions About TIRF Medication Guides

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[1]	
	n	%	n	%	n	%
Question 24: How much of the Medication Guide did you understand?[2]						
All of it	96	57.8	0	0.0	96	57.5
Most of it	57	34.3	1	100.0	58	34.7
Some of it	13	7.8	0	0.0	13	7.8
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 17 or ***No*** or ***I don't know*** to Question 22)	24		1		25	
Question 25: Did someone offer to explain the Medication Guide to you?[2]						
Yes	104	60.5	0	0.0	104	60.1
No	53	30.8	1	100.0	54	31.2
I don't know	15	8.7	0	0.0	15	8.7
N/A (answered ***No*** or ***I don't know*** to Question 17)	18		1		19	
Question 26: Who offered to explain the Medication Guide to you? (Select all that apply.)[2]						
The doctor or another healthcare professional in the doctor's office	64	61.5	0	0.0	64	61.5
The pharmacist where the TIRF medicine prescription was filled	93	89.4	0	0.0	93	89.4
Someone else (specify the type of person but not his/her name)[4]	8	7.7	0	0.0	8	7.7
N/A (answered ***No*** or ***I don't know*** to Question 17 or ***No*** or ***I don't know*** to Question 25)	86		2		88	

(continued)

Table 5. Responses to Questions About TIRF Medication Guides

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[1]	
	n	%	n	%	n	%
Question 27: Did you accept the offer to have the Medication Guide explained to you?[2]						
Yes	53	51.0	0	0.0	53	51.0
No	48	46.2	0	0.0	48	46.2
I don't know	3	2.9	0	0.0	3	2.9
N/A (answered ***No*** or ***I don't know*** to Question 17 or ***No*** or ***I don't know*** to Question 25)	86		2		88	
Question 28: How much of the explanation did you understand? [2]						
All of it	44	83.0	0	0.0	44	83.0
Most of it	8	15.1	0	0.0	8	15.1
Some of it	1	1.9	0	0.0	1	1.9
None of it	0	0.0	0	0.0	0	0.0
I don't know	0	0	0	0.0	0	0.0
N/A (answered ***No*** or ***I don't know*** to Question 17 or ***No*** or ***I don't know*** to Question 25 or ***No*** or ***I don't know*** to Question 27)	137		2		139	
Question 29: Did you or do you have any questions about the information in the Medication Guide? [2]						
Yes[5]	7	4.1	0	0.0	7	4.0
No	163	94.8	0	0.0	163	94.2
I don't know	2	1.2	1	100.0	3	1.7
N/A (answered ***No*** or ***I don't know*** to Question 17)	18		1		19	

[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] Verbatim texts for other time receiving Medication Guide (Question 21) from the pharmacy are presented in Listing 1
[4] Verbatim texts for other persons offering to explain the Medication Guide (Question 26) are presented in Listing 2
[5] Questions about the information in the Medication Guide (Question 29) are presented in Listing 3

The categorized responses to Question 21, 26 and 29 referenced in Table 5 are shown in Table 6, Table 7, and Table 8, respectively.

Table 6. Categorized Responses To Question 21 (Most recent time receiving Medication Guide for the TIRF medicine from the pharmacy)

Response (Categorized Type) [2]	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[1]	
	n	%	n	%	n	%
Sometimes	7	3.7	0	0.0	7	3.6

[1] Number of eligible respondents completing the survey (See Table 1).
[2] Categorization scheme of the verbatim responses is shown in Listing 1.
[3] Each category is only counted once per patient

Table 7. Categorized Responses To Question 26 (Other person offering explanation of the Medication Guide)

Response (Categorized Type) [2]	Patients N=190		Caregivers N=2		Patients & Caregivers N=192[1]	
	N[3]	%	N[3]	%	N[3]	%
Family	3	1.6	0	0.0	3	1.6
Pharmaceutical Rep	4	2.1	0	0.0	4	2.1
Pharmacy	1	0.5	0	0.0	1	0.5

[1] Number of eligible respondents completing the survey (See Table 1).
[2] Categorization scheme of the verbatim responses is shown in Listing 2.
[3] Each category is only counted once per patient

Table 8. Categorized Responses To Question 29 (Questions about the information in the Medication Guide)

Response (Categorized Type) [2]	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[1]	
	n	%	n	%	n	%
Education	2	1.0	0	0.0	2	1.0
Side Effects	1	0.5	0	0.0	1	0.5
Placement of medication	1	0.5	0	0.0	1	0.5
Oral Side Effects	1	0.5	0	0.0	1	0.5
Disposal	1	0.5	0	0.0	1	0.5
N/A	1	0.5	0	0.0	1	0.5

[1] Number of eligible respondents completing the survey (See Table 1).
[2] Categorization scheme of the verbatim responses is shown in Listing 3.
[3] Each category is only counted once per patient

5.2.3 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 134 (69.8%) respondents indicated that someone at the doctor's office had offered to explain the PPAF to them, and that 113 (84.3%) of them understood all of it and 19 (14.2%) understood most of it. The PPAF was signed by 144 (75.0%) respondents; of these 144 responders, 113 reported receiving a copy of the signed PPAF.

Table 9. Responses to Questions About the Patient-Prescriber Agreement Form

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[1]	
	n	%	n	%	n	%
Question 31: Did the doctor or someone in the doctor's office explain the Patient-Prescriber Agreement Form to you?						
Yes	134	70.5	0	0.0	134	69.8
No	33	17.4	2	100.0	35	18.2
I don't know	23	12.1	0	0.0	23	12.0

(continued)

Table 9. Responses to Questions About the Patient-Prescriber Agreement Form

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[1]	
	n	%	n	%	n	%
Question 32: How much of the explanation did you understand?[2]						
All of it	113	84.3	0	0.0	113	84.3
Most of it	19	14.2	0	0.0	19	14.2
Some of it	2	1.5	0	0.0	2	1.5
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 31)	56		2		58	
Question 33: Did you sign a Patient-Prescriber Agreement Form?						
Yes	144	75.8	0	0.0	144	75.0
No	13	6.8	1	50.0	14	7.3
I don't know	33	17.4	1	50.0	34	17.7
Question 34: Did the doctor or someone in the doctor's office give you a copy of the signed Patient-Prescriber Agreement Form?[2]						
Yes	113	78.5	0	0.0	113	78.5
No	14	9.7	0	0.0	14	9.7
I don't know	17	11.8	0	0.0	17	11.8
N/A (answered ***No*** or ***I don't know*** to Question 33)	46		2		48	

[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.

5.3 KAB Survey Objectives

5.3.1 Key Risk Message Results

The focus of this section of the document is on the findings for the total respondent population.

5.3.1.1 Key Risk Message 1

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

Analysis of responses to Question 12d for Key Risk Message 1 showed that 90.1% of the respondents were aware of the risk of life-threatening breathing problems with TIRF medicines (Table 10).

Table 10. Key Risk Message 1: TIRF Medicines Can Cause Life-Threatening Breathing Problems That Can Lead To Death

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[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 statement about the TIRF medicine that was most recently prescribed for you / the patient.						
12d: TIRF medicines can cause life-threatening breathing problems that can lead to death.						
True[2]	172	90.5 (85.4, 94.3)	1	50.0 (1.3, 98.7)	173	90.1 (85.0, 93.9)
False	5	2.6	0	0.0	5	2.6
I don't know	13	6.8	1	50.0	14	7.3

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

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

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

5.3.1.2 Key Risk Message 2

Key Risk Message 2 refers to the respondents' knowledge that they should not take TIRF Medicines if they are not opioid tolerant. Three (3) questions define this key risk message (Table 11).

In response to the statement in Question 10 that TIRF medicines should only be taken by patients who are opioid tolerant, 90.6% respondents gave the correct (true) response.

The majority of respondents 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 (91.7%), and the majority also understood that it is not okay for patients to-take TIRF medicines for headache pain (70.8%).

Evidence of understanding this key risk information is further supported by the average number of 2.5 out of a possible 3 correct responses.

Table 11. Key Risk Message 2: Patients Should Not Take TIRF Medicines If They Are Not Opioid Tolerant

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	N	% (95% CI)[3]
Question 10: 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]	172	90.5 (85.4, 94.3)	2	100.0 (15.8, 100.0)	174	90.6 (85.6, 94.3)
False	5	2.6	0	0.0	5	2.6
I don't know	13	6.8	0	0.0	13	6.8
Question 11: Please answer True, False, or I don't know for the following statements:						
11a: 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]	174	91.6 (86.7, 95.1)	2	100.0 (15.8, 100.0)	176	91.7 (86.8, 95.2)
False	7	3.7	0	0.0	7	3.6
I don't know	9	4.7	0	0.0	9	4.7
Question 12: 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.						
12b: It is OK for patients to take TIRF medicines for headache pain.						
True	17	8.9	0	0.0	17	8.9
False[2]	134	70.5 (63.5, 76.9)	2	100.0 (15.8, 100.0)	136	70.8 (63.9, 77.2)
I don't know	39	20.5	0	0.0	39	20.3

(continued)

Table 11. Key Risk Message 2: Patients Should Not Take TIRF Medicines If They Are Not Opioid Tolerant

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	N	% (95% CI)[3]
Secondary Analyses: Demonstrated Understanding						
0 correct responses	3	1.6	0	0.0	3	1.6
1 correct response	10	5.3	0	0.0	10	5.2
2 correct responses	61	32.1	0	0.0	61	31.8
3 correct responses	116	61.1	2	100.0	118	61.5
Average number of correct responses	2.5	(2.3, 3.0)[4]	3.0	(1.0, 3.0)[4]	2.5	(2.3, 3.0)[4]

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

[2] Indicates the correct response(s) to each question or item 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.

5.3.1.3 Key Risk Message 3

Key Risk Message 3 refers to the patient's knowledge that TIRF medicines should be taken exactly as prescribed by the healthcare provider. Three (3) questions define this key risk message. (Table 12).

Less than half (42.7%) of respondents understood that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine. However, all patients (100%) understood that TIRF medicines should be taken exactly as prescribed by the doctor and 82.3% of respondents knew that is not OK to take TIRF medicines for short-term pain that will go away in a few days.

Evidence of understanding this key risk information is further supported by the average number of 2.3 out of a possible 3 correct responses.

Table 12. Risk Message 3: TIRF Medicines Should Be Taken Exactly As Prescribed By The Healthcare Provider

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[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 each of the following statements.						
11b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.						
True[2]	82	43.2 (36.0, 50.5)	0	0.0	82	42.7 (35.6, 50.0)
False	47	24.7	0	0.0	47	24.5
I don't know	61	32.1	2	100.0	63	32.8
Question 12: 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.						
12c: TIRF medicines should be taken exactly as prescribed by the doctor.						
True[2]	190	100.0 (98.1, 100.0)	2	100.0 (15.8, 100.0)	192	100.0 (98.1, 100.0)
False	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0
Question 16: 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.						
16b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.						
True	10	5.3	0	0.0	10	5.2
False[2]	157	82.6 (76.5, 87.7)	1	50.0 (1.3, 98.7)	158	82.3 (76.1, 87.4)
I don't know	23	12.1	1	50.0	24	12.5

(continued)

Table 12. Risk Message 3: TIRF Medicines Should Be Taken Exactly As Prescribed By The Healthcare Provider

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	N	% (95% CI)[3]
Secondary Analysis: Demonstrated Understanding						
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	26	13.7	1	50.0	27	14.1
2 correct responses	89	46.8	1	50.0	90	46.9
3 correct responses	75	39.5	0	0.0	75	39.1
Average number of correct responses	2.3	(2.1, 3.0)[4]	1.5	(0.1, 3.0)[4]	2.3	(2.1, 3.0)[4]

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

[2] Indicates the correct response(s) to each question or item 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.

5.3.1.4 Key Risk Message 4

Key Risk Message 4 refers to the patient's knowledge that they must not switch TIRF medicines without talking to a healthcare provider. (Table 13)

The majority of respondents (96.9%) understood that it is not safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.

Table 13. 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=190		Caregivers n=2		Patients & Caregivers N=192[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 each of the following statements.						
11c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first						
True	1	0.5	0	0.0	1	0.5
False[2]	185	97.4 (94.0, 99.1)	1	50.0 (1.3, 98.7)	186	96.9 (93.3, 98.8)
I don't know	4	2.1	1	50.0	5	2.6

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

5.3.1.5 Key Risk Message 5

Key Risk Message 5 refers to the patient's knowledge that TIRF medicines should not be given to anyone else even if they have the same symptoms (Table 14).

All (100%) respondents understood that a patient may not give TIRF medicines to another person if they have the same symptoms as the patient, and 97.9% understood that selling or giving away TIRF medicines is against the law.

Evidence of understanding this key risk information is further supported by the average number of 2.0 out of a possible 2 correct responses.

Table 14. Key Risk Message 5: Patients Should Not Give TIRF Medicines To Anyone Else Even If They Have The Same Symptoms

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[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 each of the following statements.						
11d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.						
True	0	0.0	0	0.0	0	0.0
False[2]	190	100.0 (98.1, 100.0)	2	100.0 (15.8, 100.0)	192	100.0 (98.1, 100.0)
I don't know	0	0.0	0	0.0	0	0.0
Question 16: 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.						
16a: Selling or giving away TIRF medicines is against the law.						
True[2]	186	97.9 (94.7, 99.4)	2	100.0 (15.8, 100.0)	188	97.9 (94.8, 99.4)
False	3	1.6	0	0.0	3	1.6
I don't know	1	0.5	0	0.0	1	0.5
Secondary Analysis: Demonstrated Understanding						
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	4	2.1	0	0.0	4	2.1
2 correct responses	186	97.9	2	100.0	188	97.9
Average number of correct responses	2.0	(1.8, 2.0)[4]	2.0	(0.4, 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 item 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.

5.3.1.6 Key Risk Message 6

Key Risk Message 6 refers to the patient's knowledge that TIRF medicines should be stored in a safe place away from children and properly disposed (Table 15).

All (100%) respondents understood that TIRF medicines should be stored in a safe place out of the reach of children. The majority of respondents understood that TIRF medicines must be

disposed of as described in the specific product's Medication Guide (95.8%); a TIRF medicine can cause an overdose and death in any child who takes it (90.6%); and that they should get emergency help right way (89.1%) when asked, "What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine?"

Evidence of understanding this key risk information is further supported by the average number of 3.8 out of a possible 4 correct responses.

Table 15. Key Risk Message 6: TIRF Medicines Should Be Stored In A Safe Place Away From Children And Properly Disposed

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[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 statement about the TIRF medicine that was most recently prescribed for you / the patient.						
12a: TIRF medicines should be stored in a safe place out of the reach of children.						
True[2]	190	100.0 (98.1, 100.0)	2	100.0 (15.8, 100.0)	192	100.0 (98.1, 100.0)
False	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0
Question 16: 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.						
16c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.						
True[2]	182	95.8 (91.9, 98.2)	2	100.0 (15.8, 100.0)	184	95.8 (92.0, 98.2)
False	2	1.1	0	0.0	2	1.0
I don't know	6	3.2	0	0.0	6	3.1
16e: A TIRF medicine can cause an overdose and death in any child who takes it.						
True[2]	173	91.1 (86.1, 94.7)	1	50.0 (1.3, 98.7)	174	90.6 (85.6, 94.3)
False	4	2.1	0	0.0	4	2.1
I don't know	13	6.8	1	50.0	14	7.3

(continued)

Table 15. Key Risk Message 6: TIRF Medicines Should Be Stored In A Safe Place Away From Children And Properly Disposed

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	N	% (95% CI)[3]
Question 13: 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]	170	89.5 (84.2, 93.5)	1	50.0 (1.3, 98.7)	171	89.1 (83.8, 93.1)
Do nothing	0	0.0	0	0.0	0	0.0
Wait an hour and see if the person is OK	6	3.2	0	0.0	6	3.1
I don't know	14	7.4	1	50.0	15	7.8
Secondary Analyses: Demonstrated Understanding						
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	6	3.2	1	50.0	7	3.6
3 correct responses	33	17.4	0	0.0	33	17.2
4 correct responses	151	79.5	1	50.0	152	79.2
Average number of correct responses	3.8	(3.5, 4.0)[4]	3.0	(1.0, 4.0)[4]	3.8	(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 item 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.

5.3.2 Other Survey Questions

5.3.2.1 Additional Questions About TIRF Medicines Safety

Table 16 summarizes the respondents' answers to additional questions beyond those associated with the key risk messages. These questions assessed whether the patient had been informed of the risks and possible side effects, indications, usage, and storage, and the availability of TIRF medicines through the TIRF REMS Access Program.

Respondents were aware of the risks associated with TIRF medicines regarding side effects (85.9%).

Most respondents (67.7% to 89.6%) were aware of the clinical conditions for using TIRF medicines; however, the awareness was low regarding use in chronic non-cancer pain with only 24.5% of respondents correctly responding false.

The majority of patients were told by their doctor, nurse, or other healthcare provider how to use their TIRF medicine (93.8%) and how to properly store the medicine (80.7%). Half (50.5%) of all patients understood that TIRF medicines are only available through the TIRF REMS Access program.

Table 16. Responses to Additional Questions about the Safe Use of TIRF Medicines

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[1]	
	n	%	n	%	N	%
Question 8: 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	165	86.8	0	0.0	165	85.9
No	21	11.1	2	100.0	23	12.0
I don't know	4	2.1	0	0.0	4	2.1
Question 9: For which of the following conditions should I use a TIRF medicine?						
9a: Headache or migraine pain						
Yes	29	15.3	0	0.0	29	15.1
No[2]	138	72.6	2	100.0	140	72.9
I don't know	23	12.1	0	0.0	23	12.0
9b: Breakthrough pain from cancer						
Yes[2]	132	69.5	2	100.0	134	69.8
No	52	27.4	0	0.0	52	27.1
I don't know	6	3.2	0	0.0	6	3.1
9c: Dental pain						
Yes	3	1.6	0	0.0	3	1.6
No[2]	170	89.5	2	100.0	172	89.6
I don't know	17	8.9	0	0.0	17	8.9

(continued)

Table 16. Responses to Additional Questions about the Safe Use of TIRF Medicines

Question	Patients n=190		Caregivers n=2		Patients & Caregivers N=192[1]	
	n	%	n	%	N	%
9d: Acute or post-operative pain						
Yes	38	20.0	2	100.0	40	20.8
No[2]	130	68.4	0	0.0	130	67.7
I don't know	22	11.6	0	0.0	22	11.5
9e: Chronic non-cancer pain						
Yes	136	71.6	0	0.0	136	70.8
No[2]	45	23.7	2	100.0	47	24.5
I don't know	9	4.7	0	0.0	9	4.7
Question 14: 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?						
Yes	179	94.2	1	50.0	180	93.8
No	11	5.8	1	50.0	12	6.3
I don't know	0	0.0	0	0.0	0	0.0
Question 15: 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	155	81.6	0	0.0	155	80.7
No	31	16.3	2	100.0	33	17.2
I don't know	4	2.1	0	0.0	4	2.1
16d: TIRF medicines are only available to patients through a special program (called the TIRF REMS Access program).						
True[2]	97	51.1	0	0.0	97	50.5
False	23	12.1	0	0.0	23	12.0
I don't know	70	36.8	2	100.0	72	37.5

[1] Number of eligible respondents completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or item within a question.

5.3.3 Analyses of Subpopulations

To assess further patients' understanding of key risk messages, subgroup analyses as described in Section 4.1.2 were conducted. All results are similar to the results in the primary population, and no trends are evident. The full set of subgroup analysis tables is provided in Appendix B.

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

Among all survey respondents (N=198), 15 patients reported an adverse event, product complaint, and or medical information requests associated with the use of TIRF medicines during phone completions of this survey (Appendix B: Listing 4). A total of 7 adverse events were reported as follows: 3 patients, oral side effects affecting the mouth or teeth and gums; 1 patient, dependency on TIRF medication followed by withdrawal symptoms; 1 patient cancer (site not specified) since using TIRF medication (duration of exposure not provided); 1 patient unusual side effects (details not available) for which the patient had contacted the manufacturer; and 1 patient, using TIRF medicine for pain but not for breakthrough pain.

No reports of adverse events, product complaints, and or medical information requests were reported in the free text fields of surveys completed online by respondents

Table 17. Respondent Report of Adverse Events, Product Complaints, or Medical Information Requests During Survey

Question	Patients n=192[1]		Caregivers n=6[1]		Patients & Caregivers N=198[1]	
	n	%	n	%	N	%
Respondent spontaneously reported an adverse event, product complaint, or medical information request during the course of this survey.						
Yes[2]	15	7.7	0	0.0	15	7.6
No	181	92.3	2	100.0	183	92.4

[1] All respondents who took the survey regardless of eligibility.

[2] There were 7 adverse events, 1 product complaint, and 7 medical information requests. Verbatim text of adverse events or product complaints is given in Appendix B, Listing 4.

Table 18. Categorized Reported Adverse Events, Product Complaints, or Medical Information Requests

Response (Categorized Type) [2]	All Respondents N=198[1]	
	N[3]	%
Cancer, Pain	1	0.5
Abuse	1	0.5
Disposal	1	0.5
Education	2	1.0
Oral side effects	4	2.0
Pain	1	0.5
Placement of medication	1	0.5
Side effects	1	0.5
Unusual side effects	1	0.5
Product complaint	1	0.5
Death	1	0.5

[1] All respondents who took the survey regardless of eligibility.
[2] Categorization scheme of the verbatim responses is shown in Appendix B, Listing 4.
[3] Each category is only counted once per patient/caregiver

5.5 Discussion, Conclusions, and Recommendations

The specific goals of the TIRF medicines patient KAB survey were to evaluate the level of knowledge and assess the attitudes and behavior of patients and 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. The survey also included questions about whether patients received, read, and understood the product-specific Medication Guide and the PPAF.

Based on the number of prescriptions filled during the 90 days prior to 12 September 2012, the national pharmacy chain network partner identified 1112 possible participants. All of these participants were sent a survey invitation letter.

The screening criteria determined that 192 of the responders were eligible for participation in this survey; all 192 responders completed the survey. Although, the survey had a target of 300

completed responders, the pool of 1112 patients/caregivers, who were mailed the invitation, was small. The response of 192 completed surveys from this limited pool is within the expected response rate to mailed invitations. To maximize participation in the survey, additional recruitment methodology and or inclusion criteria will be evaluated and considered in future survey waves.

Several questions tested respondents' level of awareness of conditions for which TIRF medicines may be used. Most respondents were aware of permitted conditions for use of TIRF medicines. However, 70.8% of respondents were unaware that use in non-cancer pain is not a recommended indication. Use in headache pain was correctly identified by 136 (70.8%) patients as not to be appropriate. Lastly, the majority of respondents were aware that TIRF medicines should only be taken by patients who are opioid-tolerant.

A series of questions probed respondents' understanding of how to take TIRF medications. Although 100% of respondents understood that TIRF medicines should be taken exactly as prescribed, only 82 (42.7%) responders were aware that if a patient stopped taking round-the-clock opioid pain medication, they also needed to stop taking TIRF medicines. Most respondents (96.9%) were aware that it is not safe to switch to another medicine containing fentanyl without consulting with their HCP. All (100%) respondents knew they were not to share TIRF medicines with another person. All (100%) respondents were aware of the need for safely storing TIRF medicines.

The analyses of responses to questions defining each of the 6 key risk messages demonstrated that most respondents were well informed about the risks and safe use criteria associated with use of TIRF medicines.

Overall, this survey shows that the ongoing patient-oriented educational process is meeting its objectives in that the majority of patients completing the survey were aware of the key issues related to their use of a TIRF medication.

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)** **Archimedes Pharma US Inc.,** **Cephalon, Inc.,** **Endo Pharmaceuticals Inc.,** **Insys Therapeutics,** **Meda Pharmaceuticals,** **Mallinckrodt (a Covidien Company),** **Par Pharmaceutical, Inc.,** **ProStrakan, Inc., and** **Sandoz Inc.**
VERSION:	**3.0**
DATE:	**10 SEP 2012**
APPROVED:	**07 SEP 2012**

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LIST OF APPENDICES

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 Manager
PPAF	Patient-Prescriber Agreement Form
REALM	Rapid Estimate of Adult Literacy in Medicine
REMS	Risk Evaluation and Mitigation Strategy
SERP	Safety Event Reporting Plan
TIRF	Transmucosal Immediate Release Fentanyl
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation

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 already tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys™, and the generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Archimedes Pharma US Inc., Cephalon, Inc., Endo Pharmaceuticals Inc., Insys Therapeutics, Meda Pharmaceuticals, Mallinckrodt (a Covidien Company), Par Pharmaceutical, Inc., ProStrakan, Inc., and Sandoz Inc.

The Food and Drug Administration (FDA) has determined that a 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 Survey Design

This survey will be conducted among a sample of patients who have filled a prescription for a TIRF medicine within the past 3 months prior to survey launch and their caregivers. 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.

4.1.1 Qualitative Research on the Survey

In order to effectively evaluate the patient/caregiver survey prior to fielding the surveys, qualitative research will be performed on the survey with a sample of patients. The qualitative research assesses comprehension among participants of the words and phrases used in the survey questions and response options.

Qualitative research will be performed with eight (8) patients who meet pre-determined eligibility criteria for participation in the qualitative research interviews. The purpose of the qualitative research is to identify any terms, questions, or topics in the survey that require clarification or revision based on any areas of confusion or miscomprehension by participants interviewed.

Participants are primarily recruited through a database of patients at a research facility who are interested in being included in market research. To ensure the appropriateness of the survey for all literacy levels, attempts are made to recruit at least half of the participants to have less than or equal to a 12th grade education.

As part of the overall interview, participants are administered a REALM® (Rapid Estimate of Adult Literacy in Medicine[1]) to assess health literacy level. Participants are also recruited to represent a mix of race and gender.

4.1.2 Questions and Statements on REMS Goals

The KAB items of the questionnaire are 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 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,” “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

[1] Davis TC, Long SW, Jackson RH, Mayeaux EJ, George RB, Murphy PW, Crouch MA. Rapid estimate of adult literacy in medicine: a shortened screening instrument. Fam Med. 1993 Jun;25(6):391-5.

- 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 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 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).

<table>
<tr><td colspan="3"><u>Key Risk Message 1</u>: TIRF medicines can cause life-threatening breathing problems that can lead to death.</td></tr>
<tr><td>Question No.</td><td>Question</td><td>Desired response</td></tr>
<tr><td rowspan="2">12d</td><td colspan="2">Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.</td></tr>
<tr><td>TIRF medicines can cause life-threatening breathing problems that can lead to death.</td><td>TRUE</td></tr>
</table>

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:		
10	TIRF medicines should only be taken by patients who are opioid tolerant.	**TRUE**
Please answer True, False, or I don't know for each of the following statements.		
11a	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**
Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
12b	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**
Please answer True, False, or I don't know for each of the following statements.		
11b	If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.	**TRUE**
Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
12c	TIRF medicines should be taken exactly as prescribed by the doctor.	**TRUE**
16b	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**
11c	Please answer True, False, or I don't know for each of the following statements.	
	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**
Please answer True, False, or I don't know for each of the following statements.		
11d	A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	**FALSE**
Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
16a	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**
Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
12a	TIRF medicines should be stored in a safe place out of the reach of children.	**TRUE**
16c	TIRF medicines must be disposed of as described in the specific product's Medication Guide.	**TRUE**
16e	A TIRF medicine can cause an overdose and death in any child who takes it.	**TRUE**

13	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.**

4.1.3 Additional Questions

Questions about the requirements of the TIRF REMS, and receipt and understanding of the Medication Guides and Patient-Prescriber Agreement Form 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.

4.2 Subject Recruitment

Patients will be recruited through a direct letter program. Patients will be invited through a national pharmacy chain network partner or pharmacy benefits management (PBM) partner, which each have 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 3 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 US Postal Service.

The invitation will indicate that participants will receive a $25 gift card for completing the survey. Each invitation will also include a unique ID code and directions for accessing the survey either via the Internet or by telephone through an interviewer at the Survey Coordinating Center. The unique ID code will be used to identify the manufacturer of the most recent TIRF prescription that the patient filled.

A random sample of patients who have filled a prescription for a TIRF medicine within the last 90 days will be chosen from the pharmacy partner'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 approximately 10 business days after the first mailing, 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 not achieved within 10 additional business days, 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 another 10 days, then a new random sample of patients may be selected. The 10 day intervals described above 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 $25 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.

4.2.1 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 first 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.

Precision of Estimated Rates of Understanding with a Sample Size of 300 (2-sided 95% Confidence Interval)

Estimated Rate of Understanding	Estimated Confidence Interval	
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
- Patients who have filled a TIRF medicine prescription within the past 3 months prior to survey launch
- Caregivers 18 years of age or older who care for patients who are unable to take the survey for themselves
- Patients or caregivers who are able to complete the survey in English

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, Archimedes Pharma US Inc., Cephalon, Inc., Endo Pharmaceuticals Inc., Insys Therapeutics, Meda Pharmaceuticals, Mallinckrodt (a Covidien Company), Par Pharmaceutical, Inc., ProStrakan, Inc., Sandoz Inc., United BioSource Corporation, Teva Pharmaceuticals, Ltd., 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 five 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. 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. 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 interviews.

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 respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents who completed the survey
- 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)
- Frequency distribution of responses to each question (the number of respondents who give each answer to each question)

- Percent of respondents selecting desired response to each question relating to each key risk message and 95% confidence interval

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 respondents 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 Reporting Plan (SERP). Additional detail regarding processes for adverse event reporting will be specified in the SERP.

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 $25 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 needed 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 phone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by phone 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 phone 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

- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines or a free-text response).

- **[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 ONLINE/PHONE SURVEY CONTENT]

[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 **(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.

[ONLINE ONLY]How We Use Your Information

[PHONE ONLY] 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 $25 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.

[ONLINE ONLY] How We Protect Your Privacy

[PHONE ONLY]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). Your choice to allow the manufacturers of TIRF medicines to use your information is entirely voluntary, but necessary to take part in this survey.

[ONLINE ONLY] How to Learn More About Transmucosal Immediate Release Fentanyl Medicines

[ONLINE ONLY] 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.

[PHONE ONLY] 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.

If you have questions about your rights as a research participant or related concerns, you may contact the IRB at (b) (4). **[ONLINE ONLY]** 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.

Thank you for your participation in this survey.

[END PREAMBLE 1]

1. Do you agree to take part in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Within the last 3 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 3 months? As a reminder, 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. Have you ever taken part in a survey about a TIRF medicine before?

   - ○ Yes **[TERMINATE ONLY IN ALL SUBSEQUENT WAVES]**
   - ○ No
   - ○ I don't know **[TERMINATE ONLY IN ALL SUBSEQUENT WAVES]**

5. 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]**

6. **[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

7. 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]**
- ○ Archimedes Pharma US Inc.**[TERMINATE]**
- ○ Cephalon, Inc. **[TERMINATE]**
- ○ Endo Pharmaceuticals Inc. **[TERMINATE]**

- Insys Therapeutics**[TERMINATE]**
- Mallinckrodt (a Covidien Company) **[TERMINATE]**
- Meda Pharmaceuticals **[TERMINATE]**
- Par Pharmaceutical, Inc.**[TERMINATE]**
- ProStrakan, Inc. **[TERMINATE]**
- Sandoz Inc. **[TERMINATE]**
- Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- United BioSource Corporation**[TERMINATE]**
- McKesson Specialty Care Solutions**[TERMINATE]**
- RelayHealth**[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 answer to any of the following questions please respond "I don't know" instead of guessing the correct response.

[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 answer to any of the following questions please respond "I don't know" instead of guessing the correct response.

8. **[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

9. **[PATIENT]** For which of the following conditions should I use a TIRF medicine?

[CAREGIVER] For which of the following conditions should the person I take care of use a TIRF medicine?

	[RANDOMIZE LIST]	**Yes**	**No**	**I don't know**
9a.	Headache or migraine pain	○	○	○
9b.	Breakthrough pain from cancer	○	○	○
9c.	Dental pain	○	○	○
9d.	Acute or post-operative pain	○	○	○
9e.	Chronic non-cancer pain	○	○	○

10. 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

11. Please answer True, False, or I don't know for each of the following statements.

	[RANDOMIZE LIST]	True	False	I don't know
11a.	Opioid tolerant means that a patient is already taking other opioid pain medicines around the clock and their body is used to these medicines.	○	○	○
11b.	If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.	○	○	○
11c.	It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	○	○	○
11d.	A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	○	○	○

12. **[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
12a.	TIRF medicines should be stored in a safe place out of the reach of children.	○	○	○
12b.	It is OK for patients to take TIRF medicines for headache pain.	○	○	○
12c.	TIRF medicines should be taken exactly as prescribed by the doctor.	○	○	○
12d.	TIRF medicines can cause life-threatening breathing problems that can lead to death.	○	○	○

13. What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)

[RANDOMIZE LIST]

- o Wait an hour and see if the person is OK.
- o Get emergency help right away.
- o Do nothing.
- o I don't know

14. **[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

15. **[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

16. **[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**
16a.	Selling or giving away TIRF medicines is against the law.	○	○	○
16b.	It is OK to take TIRF medicines for short-term pain that will go away in a few days.	○	○	○
16c.	TIRF medicines must be disposed of as described in the specific product's Medication Guide.	○	○	○
16d.	TIRF medicines are only available to patients through a special program (called the TIRF REMS Access program).	○	○	○
16e.	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 or doctor.

[END PREAMBLE 3]

17. **[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]**

18. **[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 Q20]**
- ○ I don't know **[GO TO Q20]**

19. **[PATIENT]** When was the Medication Guide given to you?

[CAREGIVER] When was the Medication Guide given to you or the patient?

- ○ 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

20. **[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 Q22]**
- ○ I don't know **[GO TO Q22]**

21. **[PATIENT]** When was the most recent time that you received a Medication Guide for the TIRF medicine at the pharmacy?

[CAREGIVER] When was the most recent time that you or the patient received 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

22. Did you read the Medication Guide?

- ○ Yes
- ○ No **[GO TO Q25]**
- ○ I don't know **[GO TO Q25]**

23. How much did you read?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ I don't know

24. 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

25. Did someone offer to explain the Medication Guide to you?

- ○ Yes
- ○ No **[GO TO Q29]**
- ○ I don't know **[GO TO Q29]**

26. Who offered to explain the Medication Guide to you? (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)

_____

27. Did you accept the offer to have the Medication Guide explained to you?

- ○ Yes
- ○ No **[GO TO Q29]**
- ○ I don't know **[GO TO Q29]**

28. How much of the explanation did you understand?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ None of it
- ○ I don't know

29. 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]**

30. 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]

31. Did the doctor or someone in the doctor's office explain the Patient-Prescriber Agreement Form to you?

- ○ Yes
- ○ No **[GO TO Q33]**
- ○ I don't know **[GO TO Q33]**

32. How much of the explanation did you understand?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ None of it
- ○ I don't know

33. **[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]**

34. 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.

35. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

36. 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

37. What is the main language you speak at home? (Please select only one.)

- ○ English
- ○ French
- ○ Spanish
- ○ Portuguese
- ○ Italian
- ○ German
- ○ Chinese
- ○ Japanese
- ○ Korean
- ○ Other
- ○ Prefer not to answer

38. Are you Hispanic or Latino?

- ○ Yes
- ○ No
- ○ Prefer not to answer

39. For informational purposes only, which of the following U.S. census categories best describes your race? (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
- ○ Other
- ○ Prefer not to answer

40. 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 $25 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.

41. 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: _____

LAST NAME: _____

ADDRESS: **[MULTILINE INPUT]**

CITY: _____

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: _____

[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.

42. Do you want to provide your telephone number?

○ Yes

○ No **[SKIP TO CLOSING 3]**

Telephone: _____

[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] for your prescription needs. We are contacting you to invite you to participate in a survey being conducted by the manufacturers of Transmucosal Immediate Release Fentanyl medicines (TIRF medicines), as required by the FDA. The purpose of the survey is to find out if patients and/or their caregivers understand important information related to taking these medicines. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys™, and the generic versions of any of these brands.

The survey is being administered by United BioSource Corporation, on behalf of the manufacturers of TIRF medicines: Archimedes Pharma US Inc., Cephalon, Inc., Endo Pharmaceuticals Inc., Insys Therapeutics, Meda Pharmaceuticals, Mallinckrodt (a Covidien Company), Par Pharmaceutical, Inc., ProStrakan, Inc., and Sandoz Inc. Survey participants must be 18 years of age or older. A caregiver may complete the survey on behalf of patients who are unable to take the survey for themselves. Eligible individuals who complete the survey will be sent a $25 gift card to thank them for their time. The survey will take about 20 minutes.

If you are interested in participating and want to find out if you are eligible,

- Go to www.XXX.com* any time, or
- Call 1-877-379-3297, 8 a.m. to 10 p.m. Eastern Time, Monday through Friday.

Please have this letter with you when you take the survey. You will be asked to give this unique code prior to starting the survey: **[CODE_ID]**.

The survey asks questions about the type of information you received about your TIRF medication and where you get your medication information.

You do not have to take part in this survey; the decision to participate is entirely yours. Your privacy will be strictly guarded. 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 a TIRF medicine.

Thank you in advance for your help with this important survey.

Sincerely,

[PHARMACY]

* 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.

Appendix B Patient Survey Listings and Subanalyses Tables

Patient Listings

Listing 1 CATEGORIZATION OF VERBATIM RESPONSES TO QUESTION 21 (Most recent time receiving Medication Guide for the TIRF medicine from the pharmacy)

Verbatim Response	Categorized Response
Every 3 or 4 months	Sometimes
Occasionnally but not every time	Sometimes
Depends on pharmacist. Get them almost every time.	Sometimes
Every couple of months	Sometimes
I have received the Medication Guide more than once but not each time a prescription is filled.	Sometimes
They ask if I need one and occasionally I will take one.	Sometimes
I believe I received it a few times but i don't think I get one each time	Sometimes

Listing 2 CATEGORIZATION OF VERBATIM RESPONSES TO QUESTION 26 (Other person offering explanation of the Medication Guide)

Verbatim Response	Categorized Response
Her son	Family
My husband	Family
Person from company on phone	Pharmaceutical Rep
Pharmaceutical representative	Pharmaceutical Rep
pharmacy tech	Pharmacy
The drug rep who solicited this medication to the practice	Pharmaceutical Rep
The manufacturer contacted me by phone when I started taking Actiq	Pharmaceutical Rep
The patient's wife is a nurse	Family

Listing 3 CATEGORIZATION OF VERBATIM RESPONSES TO QUESTION 29 (Questions about the information in the Medication Guide)

Verbatim Response	Categorized Response
Is there any ARTIFICIAL SUGAR in the product? Exactly how much sugar is in the product? After reading about absorption rates...so; only about 40%-60% of actual medicine is absorbed into person body through mucosa of the cheek?	Education
Are there serious side effects?	Side effects
Exact placement of tab in mouth	Placement of medication
How is Actiq still on the market when it has been shown to distroy peoples teeth even with proper dental care and you admit that even in the medication guide?	Oral side effects
How to understand the actual chemical structure diagram & symbols. I am not a chemist, but would like to know what the chemical symbols mean.	Education
I currently do not have questions but on beginning the medication both my wife and I had questions and concerns that where addressed at that time.	N/A
Question regarding proper disposal of container(s) holding buccal tablets.	Disposal

Listing 4 CATEGORIZATION OF REPORTED SAFETY EVENTS OR PRODUCT COMPLAINTS

Verbatim Response	Categorized Response
I got put on the medication because I shattered my jaw in a accident. I have a hard time chewing because of my facial injury. I have developed cancer since being on the medication."	Cancer, Pain
I was hooked on this medication. Withdrawal was terrible. I became a mean and hateful person without it. It was a horrible experience. My son took the medications away from me.	Abuse
I'm taking it for breakthrough pain but not cancer pain.	Pain
My dentist bill is crazy from taking the medicine my mouth looks like a junkyard.	Oral side effects
Patient has had this teeth decaying for a while. He was told by his doctor that this is normal due to the sugar in the medication.	Oral side effects
That lollypop is rotting my teeth and gums.	Oral side effects
This patient completed her survey without mentioning an adverse event(s). Once the survey was completed, PT asked if she could ask me a question. PT asked how/to whom she would report unusual side effects to her TIRF medication. Since the survey had been completed, I directed PT to her doctor. PT stated that she has called her doctor with these side effects and was told that they would be reported to the manufacturer. PT also stated that she called the manufacturer about these side effects and received a return call that 'gee, we've never heard that before'. PT inquired whether she should contact the FDA with this information.	Unusual side effects
Is there any ARTIFICIAL SUGAR in the product? Exactly how much sugar is in the product? After reading about absorption rates...so; only about 40%-60% of actual medicine is absorbed into person body through mucosa of the cheek?	Education
Are there serious side effects?	Side Effects
Exact placement of tab in mouth	Placement of medication

Verbatim Response	Categorized Response
How is Actiq still on the market when it has been shown to distroy peoples teeth even with proper dental care and you admit that even in the medication guide?	Oral Side Effects
How to understand the actual chemical structure diagram & symbols. I am not a chemist, but would like to know what the chemical symbols mean.	Education
Question regarding proper disposal of container(s) holding buccal tablets.	Disposal
After I had been on the medication for several years	Product Complaint
$25.00 for 20 minutes. That's not a lot. The only reason I called is because I thought I could fill out the survey for my husband because he died."	Death

Patient Subanalysis Tables

TABLE 6.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES CAN CAUSE LIFE-THREATENING BREATHING PROBLEMS THAT CAN LEAD TO DEATH.

SUBGROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 15, 16 AND 17)

- **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".**

Question	S-1a Read most of Med Guide N=150		S-1b Read some or none of Med Guide N=42	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
12d: TIRF medicines can cause life-threatening breathing problems that can lead to death.				
Correct response				
True	138	92.0 (86.4, 95.8)	35	83.3 (68.6, 93.0)
Incorrect response				
False	3	2.0	2	4.8
I don't know	9	6.0	5	11.9

TABLE 7.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUBGROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 15, 16 AND 17)

- **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".**

Question	S-1a Read most of Med Guide N=150		S-1b Read some or none of Med Guide N=42	
	N	% (95% CI)	N	% (95% CI)
Question 10: 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.				
Correct response				
True	140	93.3 (88.1, 96.8)	34	81.0 (65.9, 91.4)
Incorrect response				
False	3	2.0	2	4.8
I don't know	7	4.7	6	14.3
Question 11: Please answer True, False, or I don't know for the following statements:				
11a: 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	141	94.0 (88.9, 97.2)	35	83.3 (68.6, 93.0)
Incorrect response				
False	6	4.0	1	2.4
I don't know	3	2.0	6	14.3

Question	S-1a Read most of Med Guide N=150		S-1b Read some or none of Med Guide N=42	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
12b: It is OK for patients to take TIRF medicines for headache pain.				
Correct response				
False	110	73.3 (65.5, 80.2)	26	61.9 (45.6, 76.4)
Incorrect response				
True	14	9.3	3	7.1
I don't know	26	17.3	13	31.0

TABLE 7.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUBGROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 15, 16 AND 17)

- **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".**

Demonstrated Understanding	S-1a Read most of Med Guide N=150		S-1b Read some or none of Med Guide N=42	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	3	7.1
1 correct response	5	3.3	5	11.9
2 correct responses	49	32.7	12	28.6
3 correct responses	96	64.0	22	52.4
Average number of correct responses	2.6	(2.4, 3.0)	2.3	(1.9, 3.0)

TABLE 8.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUBGROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 15, 16 AND 17)

- **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".**

Question	S-1a Read most of Med Guide N=150		S-1b Read some or none of Med Guide N=42	
	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statements:				
11b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.				
Correct response				
True	70	46.7 (38.5, 55.0)	12	28.6 (15.7, 44.6)
Incorrect response				
False	39	26.0	8	19.0
I don't know	41	27.3	22	52.4
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
12c: TIRF medicines should be taken exactly as prescribed by the doctor.				
Correct response				
True	150	100.0 (97.6, 100.0)	42	100.0 (91.6, 100.0)
Incorrect response				
False	0	0.0	0	0.0
I don't know	0	0.0	0	0.0

Question	S-1a Read most of Med Guide N=150		S-1b Read some or none of Med Guide N=42	
	N	% (95% CI)	N	% (95% CI)
Question 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
16b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.				
Correct response				
False	130	86.7 (80.2, 91.7)	28	66.7 (50.5, 80.4)
Incorrect response				
True	7	4.7	3	7.1
I don't know	13	8.7	11	26.2

TABLE 8.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUBGROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 15, 16 AND 17)

- **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".**

Demonstrated Understanding	S-1a Read most of Med Guide N=150		S-1b Read some or none of Med Guide N=42	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0
1 correct response	14	9.3	13	31.0
2 correct responses	72	48.0	18	42.9
3 correct responses	64	42.7	11	26.2
Average number of correct responses	2.3	(2.1, 3.0)	2.0	(1.6, 3.0)

TABLE 9.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: PATIENTS SHOULD NOT SWITCH FROM A TIRF MEDICINE TO ANOTHER MEDICINE THAT CONTAINS FENTANYL WITHOUT TALKING TO A HEALTHCARE PROVIDER.

SUBGROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 15, 16 AND 17)

- **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".**

Question	S-1a Read most of Med Guide N=150		S-1b Read some or none of Med Guide N=42	
	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statements:				
11c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first				
Correct response				
False	148	98.7 (95.3, 99.8)	38	90.5 (77.4, 97.3)
Incorrect response				
True	1	0.7	0	0.0
I don't know	1	0.7	4	9.5

TABLE 10.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUBGROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 15, 16 AND 17)

- **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".**

Question	S-1a Read most of Med Guide N=150		S-1b Read some or none of Med Guide N=42	
	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statements:				
11d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.				
Correct response				
False	150	100.0 (97.6, 100.0)	42	100.0 (91.6, 100.0)
Incorrect response				
True	0	0.0	0	0.0
I don't know	0	0.0	0	0.0
Question 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
16a: Selling or giving away TIRF medicines is against the law.				
Correct response				
True	147	98.0 (94.3, 99.6)	41	97.6 (87.4, 99.9)
Incorrect response				
False	3	2.0	0	0.0
I don't know	0	0.0	1	2.4

TABLE 10.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUBGROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 15, 16 AND 17)

- **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".**

Demonstrated Understanding	S-1a Read most of Med Guide N=150		S-1b Read some or none of Med Guide N=42	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0
1 correct response	3	2.0	1	2.4
2 correct responses	147	98.0	41	97.6
Average number of correct responses	2.0	(1.8, 2.0)	2.0	(1.6, 2.0)

TABLE 11.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUBGROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 15, 16 AND 17)

- **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".**

Question	S-1a Read most of Med Guide N=150		S-1b Read some or none of Med Guide N=42	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
12a: TIRF medicines should be stored in a safe place out of the reach of children.				
Correct response				
True	150	100.0 (97.6, 100.0)	42	100.0 (91.6, 100.0)
Incorrect response				
False	0	0.0	0	0.0
I don't know	0	0.0	0	0.0

Question	S-1a Read most of Med Guide N=150		S-1b Read some or none of Med Guide N=42	
	N	% (95% CI)	N	% (95% CI)
Question 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
16c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.				
Correct response				
True	147	98.0 (94.3, 99.6)	37	88.1 (74.4, 96.0)
Incorrect response				
False	1	0.7	1	2.4
I don't know	2	1.3	4	9.5
16e: A TIRF medicine can cause an overdose and death in any child who takes it.				
Correct response				
True	140	93.3 (88.1, 96.8)	34	81.0 (65.9, 91.4)
Incorrect response				
False	2	1.3	2	4.8
I don't know	8	5.3	6	14.3
Question 13: 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.	138	92.0 (86.4, 95.8)	33	78.6 (63.2, 89.7)
Incorrect response				
Do nothing.	0	0.0	0	0.0
Wait an hour and see if the person is OK.	5	3.3	1	2.4
I don't know	7	4.7	8	19.0

TABLE 11.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUBGROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 15, 16 AND 17)

- **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".**

Demonstrated Understanding	S-1a Read most of Med Guide N=150		S-1b Read some or none of Med Guide N=42	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0
2 correct responses	3	2.0	4	9.5
3 correct responses	19	12.7	14	33.3
4 correct responses	128	85.3	24	57.1
Average number of correct responses	3.8	(3.6, 4.0)	3.5	(3.0, 4.0)

TABLE 6.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES CAN CAUSE LIFE-THREATENING BREATHING PROBLEMS THAT CAN LEAD TO DEATH.

SUBGROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 24)

- **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=154		S-2b Understood Some N=13		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=25	
	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 statement about the TIRF medicine that was most recently prescribed for you.								
12d: TIRF medicines can cause life-threatening breathing problems that can lead to death.								
Correct response								
True	143	92.9 (87.6, 96.4)	9	69.2 (38.6, 90.9)	0	0.0	21	84.0 (63.9, 95.5)
Incorrect response								
False	3	1.9	1	7.7	0	0.0	1	4.0
I don't know	8	5.2	3	23.1	0	0.0	3	12.0

TABLE 7.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUBGROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 24)

- **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=154		S-2b Understood Some N=13		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=25	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: 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.								
Correct response								
True	144	93.5 (88.4, 96.8)	10	76.9 (46.2, 95.0)	0	0.0	20	80.0 (59.3, 93.2)
Incorrect response								
False	3	1.9	1	7.7	0	0.0	1	4.0
I don't know	7	4.5	2	15.4	0	0.0	4	16.0

Question	S-2a Understood All Or Most N=154		S-2b Understood Some N=13		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=25	
	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 statements:								
11a: 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	144	93.5 (88.4, 96.8)	12	92.3 (64.0, 99.8)	0	0.0	20	80.0 (59.3, 93.2)
Incorrect response								
False	6	3.9	1	7.7	0	0.0	0	0.0
I don't know	4	2.6	0	0.0	0	0.0	5	20.0
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
12b: It is OK for patients to take TIRF medicines for headache pain.								
Correct response								
False	112	72.7 (65.0, 79.6)	9	69.2 (38.6, 90.9)	0	0.0	15	60.0 (38.7, 78.9)
Incorrect response								
True	14	9.1	1	7.7	0	0.0	2	8.0
I don't know	28	18.2	3	23.1	0	0.0	8	32.0

TABLE 7.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUBGROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 24)

- **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=154		S-2b Understood Some N=13		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=25	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	1	0.6	0	0.0	0	0.0	2	8.0
1 correct response	5	3.2	1	7.7	0	0.0	4	16.0
2 correct responses	49	31.8	6	46.2	0	0.0	6	24.0
3 correct responses	99	64.3	6	46.2	0	0.0	13	52.0
Average number of correct responses	2.6	(2.4, 3.0)	2.4	(1.7, 3.0)	0	(0.0, 3.0)	2.2	(1.7, 3.0)

TABLE 8.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUBGROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 24)

- **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=154		S-2b Understood Some N=13		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=25	
	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 statements:								
11b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.								
Correct response								
True	72	46.8 (38.7, 55.0)	2	15.4 (1.9, 45.4)	0	0.0	8	32.0 (14.9, 53.5)
Incorrect response								
False	40	26.0	2	15.4	0	0.0	5	20.0
I don't know	42	27.3	9	69.2	0	0.0	12	48.0

Question	S-2a Understood All Or Most N=154		S-2b Understood Some N=13		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=25	
	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 statement about the TIRF medicine that was most recently prescribed for you.								
12c: TIRF medicines should be taken exactly as prescribed by the doctor.								
Correct response								
True	154	100.0 (97.6, 100.0)	13	100.0 (75.3, 100.0)	0	0.0	25	100.0 (86.3, 100.0)
Incorrect response								
False	0	0.0	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 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
16b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.								
Correct response								
False	132	85.7 (79.2, 90.8)	10	76.9 (46.2, 95.0)	0	0.0	16	64.0 (42.5, 82.0)
Incorrect response								
True	9	5.8	1	7.7	0	0.0	0	0.0
I don't know	13	8.4	2	15.4	0	0.0	9	36.0

TABLE 8.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUBGROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 24)

- **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=154		S-2b Understood Some N=13		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=25	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	16	10.4	3	23.1	0	0.0	8	32.0
2 correct responses	72	46.8	8	61.5	0	0.0	10	40.0
3 correct responses	66	42.9	2	15.4	0	0.0	7	28.0
Average number of correct responses	2.3	(2.1, 3.0)	1.9	(1.3, 3.0)	0	(0.0, 3.0)	2.0	(1.5, 3.0)

TABLE 9.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: PATIENTS SHOULD NOT SWITCH FROM A TIRF MEDICINE TO ANOTHER MEDICINE THAT CONTAINS FENTANYL WITHOUT TALKING TO A HEALTHCARE PROVIDER.

SUBGROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 24)

- **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=154		S-2b Understood Some N=13		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=25	
	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 statements:								
11c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first								
Correct response								
False	153	99.4 (96.4, 100.0)	11	84.6 (54.6, 98.1)	0	0.0	22	88.0 (68.8, 97.5)
Incorrect response								
True	0	0.0	1	7.7	0	0.0	0	0.0
I don't know	1	0.6	1	7.7	0	0.0	3	12.0

TABLE 10.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUBGROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 24)

- **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=154		S-2b Understood Some N=13		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=25	
	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 statements:								
11d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.								
Correct response								
False	154	100.0 (97.6, 100.0)	13	100.0 (75.3, 100.0)	0	0.0	25	100.0 (86.3, 100.0)
Incorrect response								
True	0	0.0	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 Understood All Or Most N=154		S-2b Understood Some N=13		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=25	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
16a: Selling or giving away TIRF medicines is against the law.								
Correct response								
True	151	98.1 (94.4, 99.6)	13	100.0 (75.3, 100.0)	0	0.0	24	96.0 (79.6, 99.9)
Incorrect response								
False	3	1.9	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0	1	4.0

TABLE 10.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUBGROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 24)

- **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=154		S-2b Understood Some N=13		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=25	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	3	1.9	0	0.0	0	0.0	1	4.0
2 correct responses	151	98.1	13	100.0	0	0.0	24	96.0
Average number of correct responses	2.0	(1.8, 2.0)	2.0	(1.4, 2.0)	0	(0.0, 2.0)	2.0	(1.5, 2.0)

TABLE 11.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUBGROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 24)

- **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=154		S-2b Understood Some N=13		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=25	
	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 statement about the TIRF medicine that was most recently prescribed for you.								
12a: TIRF medicines should be stored in a safe place out of the reach of children.								
Correct response								
True	154	100.0 (97.6, 100.0)	13	100.0 (75.3, 100.0)	0	0.0	25	100.0 (86.3, 100.0)
Incorrect response								
False	0	0.0	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 Understood All Or Most N=154		S-2b Understood Some N=13		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=25	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
16c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.								
Correct response								
True	149	96.8 (92.6, 98.9)	11	84.6 (54.6, 98.1)	0	0.0	24	96.0 (79.6, 99.9)
Incorrect response								
False	2	1.3	0	0.0	0	0.0	0	0.0
I don't know	3	1.9	2	15.4	0	0.0	1	4.0
16e: A TIRF medicine can cause an overdose and death in any child who takes it.								
Correct response								
True	145	94.2 (89.2, 97.3)	11	84.6 (54.6, 98.1)	0	0.0	18	72.0 (50.6, 87.9)
Incorrect response								
False	1	0.6	2	15.4	0	0.0	1	4.0
I don't know	8	5.2	0	0.0	0	0.0	6	24.0

Question	S-2a Understood All Or Most N=154		S-2b Understood Some N=13		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=25	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: 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.	140	90.9 (85.2, 94.9)	10	76.9 (46.2, 95.0)	0	0.0	21	84.0 (63.9, 95.5)
Incorrect response								
Do nothing.	0	0.0	0	0.0	0	0.0	0	0.0
Wait an hour and see if the person is OK.	6	3.9	0	0.0	0	0.0	0	0.0
I don't know	8	5.2	3	23.1	0	0.0	4	16.0

TABLE 11.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUBGROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 24)

- **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=154		S-2b Understood Some N=13		S-2c None/I don't know N=0		S-2d Did not Get or Read Medication Guide N=25	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
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	1.9	2	15.4	0	0.0	2	8.0
3 correct responses	22	14.3	3	23.1	0	0.0	8	32.0
4 correct responses	129	83.8	8	61.5	0	0.0	15	60.0
Average number of correct responses	3.8	(3.6, 4.0)	3.5	(2.6, 4.0)	0	(0.0, 4.0)	3.5	(2.9, 4.0)

TABLE 6.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

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=47		S-3b 10 to <20 min N=52		S-3c >= 20 min N=13	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
12d: TIRF medicines can cause life-threatening breathing problems that can lead to death.						
Correct response						
True	38	80.9 (66.7, 90.9)	51	98.1 (89.7, 100.0)	12	92.3 (64.0, 99.8)
Incorrect response						
False	3	6.4	0	0.0	1	7.7
I don't know	6	12.8	1	1.9	0	0.0

TABLE 7.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

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=47		S-3b 10 to <20 min N=52		S-3c >= 20 min N=13	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: 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.						
Correct response						
True	40	85.1 (71.7, 93.8)	52	100.0 (93.2, 100.0)	13	100.0 (75.3, 100.0)
Incorrect response						
False	1	2.1	0	0.0	0	0.0
I don't know	6	12.8	0	0.0	0	0.0
Question 11: Please answer True, False, or I don't know for the following statements:						
11a: 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	39	83.0 (69.2, 92.4)	49	94.2 (84.1, 98.8)	13	100.0 (75.3, 100.0)
Incorrect response						
False	4	8.5	2	3.8	0	0.0
I don't know	4	8.5	1	1.9	0	0.0

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=52		S-3c >= 20 min N=13	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
12b: It is OK for patients to take TIRF medicines for headache pain.						
Correct response						
False	36	76.6 (62.0, 87.7)	32	61.5 (47.0, 74.7)	9	69.2 (38.6, 90.9)
Incorrect response						
True	2	4.3	8	15.4	3	23.1
I don't know	9	19.1	12	23.1	1	7.7

TABLE 7.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

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=47		S-3b 10 to <20 min N=52		S-3c >= 20 min N=13	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	2	4.3	0	0.0	0	0.0
1 correct response	3	6.4	2	3.8	0	0.0
2 correct responses	14	29.8	19	36.5	4	30.8
3 correct responses	28	59.6	31	59.6	9	69.2
Average number of correct responses	2.4	(2.1, 3.0)	2.6	(2.2, 3.0)	2.7	(1.9, 3.0)

TABLE 8.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

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=47		S-3b 10 to <20 min N=52		S-3c >= 20 min N=13	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statements:						
11b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.						
Correct response						
True	18	38.3 (24.5, 53.6)	32	61.5 (47.0, 74.7)	6	46.2 (19.2, 74.9)
Incorrect response						
False	12	25.5	9	17.3	3	23.1
I don't know	17	36.2	11	21.2	4	30.8
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
12c: TIRF medicines should be taken exactly as prescribed by the doctor.						
Correct response						
True	47	100.0 (92.5, 100.0)	52	100.0 (93.2, 100.0)	13	100.0 (75.3, 100.0)
Incorrect response						
False	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=52		S-3c >= 20 min N=13	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
16b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.						
Correct response						
False	40	85.1 (71.7, 93.8)	46	88.5 (76.6, 95.6)	10	76.9 (46.2, 95.0)
Incorrect response						
True	1	2.1	2	3.8	2	15.4
I don't know	6	12.8	4	7.7	1	7.7

TABLE 8.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

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=47		S-3b 10 to <20 min N=52		S-3c >= 20 min N=13	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	6	12.8	3	5.8	2	15.4
2 correct responses	24	51.1	20	38.5	6	46.2
3 correct responses	17	36.2	29	55.8	5	38.5
Average number of correct responses	2.2	(1.9, 3.0)	2.5	(2.1, 3.0)	2.2	(1.5, 3.0)

TABLE 9.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

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=47		S-3b 10 to <20 min N=52		S-3c >= 20 min N=13	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statements:						
11c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first						
Correct response						
False	45	95.7 (85.5, 99.5)	52	100.0 (93.2, 100.0)	13	100.0 (75.3, 100.0)
Incorrect response						
True	0	0.0	0	0.0	0	0.0
I don't know	2	4.3	0	0.0	0	0.0

TABLE 10.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

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=47		S-3b 10 to <20 min N=52		S-3c >= 20 min N=13	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statements:						
11d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.						
Correct response						
False	47	100.0 (92.5, 100.0)	52	100.0 (93.2, 100.0)	13	100.0 (75.3, 100.0)
Incorrect response						
True	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0
Question 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
16a: Selling or giving away TIRF medicines is against the law.						
Correct response						
True	46	97.9 (88.7, 99.9)	52	100.0 (93.2, 100.0)	12	92.3 (64.0, 99.8)
Incorrect response						
False	0	0.0	0	0.0	1	7.7
I don't know	1	2.1	0	0.0	0	0.0

TABLE 10.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

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=47		S-3b 10 to <20 min N=52		S-3c >= 20 min N=13	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	1	2.1	0	0.0	1	7.7
2 correct responses	46	97.9	52	100.0	12	92.3
Average number of correct responses	2.0	(1.6, 2.0)	2.0	(1.7, 2.0)	1.9	(1.3, 2.0)

TABLE 11.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

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=47		S-3b 10 to <20 min N=52		S-3c >= 20 min N=13	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
12a: TIRF medicines should be stored in a safe place out of the reach of children.						
Correct response						
True	47	100.0 (92.5, 100.0)	52	100.0 (93.2, 100.0)	13	100.0 (75.3, 100.0)
Incorrect response						
False	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=52		S-3c >= 20 min N=13	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
16c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.						
Correct response						
True	45	95.7 (85.5, 99.5)	49	94.2 (84.1, 98.8)	13	100.0 (75.3, 100.0)
Incorrect response						
False	0	0.0	0	0.0	0	0.0
I don't know	2	4.3	3	5.8	0	0.0
16e: A TIRF medicine can cause an overdose and death in any child who takes it.						
Correct response						
True	44	93.6 (82.5, 98.7)	46	88.5 (76.6, 95.6)	12	92.3 (64.0, 99.8)
Incorrect response						
False	2	4.3	0	0.0	0	0.0
I don't know	1	2.1	6	11.5	1	7.7
Question 13: 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.	40	85.1 (71.7, 93.8)	48	92.3 (81.5, 97.9)	11	84.6 (54.6, 98.1)
Incorrect response						
Do nothing.	0	0.0	0	0.0	0	0.0
Wait an hour and see if the person is OK.	1	2.1	1	1.9	1	7.7
I don't know	6	12.8	3	5.8	1	7.7

TABLE 11.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

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=47		S-3b 10 to <20 min N=52		S-3c >= 20 min N=13	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
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	4	8.5	1	1.9	1	7.7
3 correct responses	4	8.5	11	21.2	1	7.7
4 correct responses	39	83.0	40	76.9	11	84.6
Average number of correct responses	3.7	(3.3, 4.0)	3.8	(3.3, 4.0)	3.8	(2.9, 4.0)

TABLE 6.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

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=2		S-4b 10 to <20 min N=62		S-4c >= 20 min N=16	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
12d: TIRF medicines can cause life-threatening breathing problems that can lead to death.						
Correct response						
True	2	100.0 (15.8, 100.0)	56	90.3 (80.1, 96.4)	14	87.5 (61.7, 98.4)
Incorrect response						
False	0	0.0	1	1.6	0	0.0
I don't know	0	0.0	5	8.1	2	12.5

TABLE 7.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

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=2		S-4b 10 to <20 min N=62		S-4c >= 20 min N=16	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: 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.						
Correct response						
True	2	100.0 (15.8, 100.0)	52	83.9 (72.3, 92.0)	15	93.8 (69.8, 99.8)
Incorrect response						
False	0	0.0	4	6.5	0	0.0
I don't know	0	0.0	6	9.7	1	6.3
Question 11: Please answer True, False, or I don't know for the following statements:						
11a: 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	2	100.0 (15.8, 100.0)	58	93.5 (84.3, 98.2)	15	93.8 (69.8, 99.8)
Incorrect response						
False	0	0.0	1	1.6	0	0.0
I don't know	0	0.0	3	4.8	1	6.3

Question	S-4a <10 min N=2		S-4b 10 to <20 min N=62		S-4c >= 20 min N=16	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
12b: It is OK for patients to take TIRF medicines for headache pain.						
Correct response						
False	2	100.0 (15.8, 100.0)	45	72.6 (59.8, 83.1)	12	75.0 (47.6, 92.7)
Incorrect response						
True	0	0.0	3	4.8	1	6.3
I don't know	0	0.0	14	22.6	3	18.8

TABLE 7.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

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=2		S-4b 10 to <20 min N=62		S-4c >= 20 min N=16	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	1	1.6	0	0.0
1 correct response	0	0.0	5	8.1	0	0.0
2 correct responses	0	0.0	18	29.0	6	37.5
3 correct responses	2	100.0	38	61.3	10	62.5
Average number of correct responses	3.0	(1.0, 3.0)	2.5	(2.2, 3.0)	2.6	(2.0, 3.0)

TABLE 8.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

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=2		S-4b 10 to <20 min N=62		S-4c >= 20 min N=16	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statements:						
11b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.						
Correct response						
True	1	50.0 (1.3, 98.7)	22	35.5 (23.7, 48.7)	3	18.8 (4.0, 45.6)
Incorrect response						
False	1	50.0	17	27.4	5	31.3
I don't know	0	0.0	23	37.1	8	50.0
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
12c: TIRF medicines should be taken exactly as prescribed by the doctor.						
Correct response						
True	2	100.0 (15.8, 100.0)	62	100.0 (94.2, 100.0)	16	100.0 (79.4, 100.0)
Incorrect response						
False	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0

Question	S-4a <10 min N=2		S-4b 10 to <20 min N=62		S-4c >= 20 min N=16	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
16b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.						
Correct response						
False	1	50.0 (1.3, 98.7)	49	79.0 (66.8, 88.3)	12	75.0 (47.6, 92.7)
Incorrect response						
True	1	50.0	4	6.5	0	0.0
I don't know	0	0.0	9	14.5	4	25.0

TABLE 8.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

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=2		S-4b 10 to <20 min N=62		S-4c >= 20 min N=16	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	12	19.4	4	25.0
2 correct responses	2	100.0	29	46.8	9	56.3
3 correct responses	0	0.0	21	33.9	3	18.8
Average number of correct responses	2.0	(0.4, 3.0)	2.1	(1.8, 3.0)	1.9	(1.4, 3.0)

TABLE 9.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

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=2		S-4b 10 to <20 min N=62		S-4c >= 20 min N=16	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statements:						
11c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first						
Correct response						
False	2	100.0 (15.8, 100.0)	59	95.2 (86.5, 99.0)	15	93.8 (69.8, 99.8)
Incorrect response						
True	0	0.0	0	0.0	1	6.3
I don't know	0	0.0	3	4.8	0	0.0

TABLE 10.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

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=2		S-4b 10 to <20 min N=62		S-4c >= 20 min N=16	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statements:						
11d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.						
Correct response						
False	2	100.0 (15.8, 100.0)	62	100.0 (94.2, 100.0)	16	100.0 (79.4, 100.0)
Incorrect response						
True	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0
Question 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
16a: Selling or giving away TIRF medicines is against the law.						
Correct response						
True	2	100.0 (15.8, 100.0)	60	96.8 (88.8, 99.6)	16	100.0 (79.4, 100.0)
Incorrect response						
False	0	0.0	2	3.2	0	0.0
I don't know	0	0.0	0	0.0	0	0.0

TABLE 10.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

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=2		S-4b 10 to <20 min N=62		S-4c >= 20 min N=16	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	2	3.2	0	0.0
2 correct responses	2	100.0	60	96.8	16	100.0
Average number of correct responses	2.0	(0.4, 2.0)	2.0	(1.7, 2.0)	2.0	(1.4, 2.0)

TABLE 11.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

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=2		S-4b 10 to <20 min N=62		S-4c >= 20 min N=16	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
12a: TIRF medicines should be stored in a safe place out of the reach of children.						
Correct response						
True	2	100.0 (15.8, 100.0)	62	100.0 (94.2, 100.0)	16	100.0 (79.4, 100.0)
Incorrect response						
False	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0

Question	S-4a <10 min N=2		S-4b 10 to <20 min N=62		S-4c >= 20 min N=16	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
16c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.						
Correct response						
True	2	100.0 (15.8, 100.0)	59	95.2 (86.5, 99.0)	16	100.0 (79.4, 100.0)
Incorrect response						
False	0	0.0	2	3.2	0	0.0
I don't know	0	0.0	1	1.6	0	0.0
16e: A TIRF medicine can cause an overdose and death in any child who takes it.						
Correct response						
True	2	100.0 (15.8, 100.0)	56	90.3 (80.1, 96.4)	14	87.5 (61.7, 98.4)
Incorrect response						
False	0	0.0	1	1.6	1	6.3
I don't know	0	0.0	5	8.1	1	6.3
Question 13: 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.	2	100.0 (15.8, 100.0)	54	87.1 (76.1, 94.3)	16	100.0 (79.4, 100.0)
Incorrect response						
Do nothing.	0	0.0	0	0.0	0	0.0
Wait an hour and see if the person is OK.	0	0.0	3	4.8	0	0.0
I don't know	0	0.0	5	8.1	0	0.0

TABLE 11.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

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=2		S-4b 10 to <20 min N=62		S-4c >= 20 min N=16	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
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	0	0.0	1	1.6	0	0.0
3 correct responses	0	0.0	15	24.2	2	12.5
4 correct responses	2	100.0	46	74.2	14	87.5
Average number of correct responses	4.0	(1.7, 4.0)	3.7	(3.3, 4.0)	3.9	(3.1, 4.0)

TABLE 6.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

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=112		S-5b Telephone N=80	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
12d: TIRF medicines can cause life-threatening breathing problems that can lead to death.				
Correct response				
True	101	90.2 (83.1, 95.0)	72	90.0 (81.2, 95.6)
Incorrect response				
False	4	3.6	1	1.3
I don't know	7	6.3	7	8.8

TABLE 7.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

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=112		S-5b Telephone N=80	
	N	% (95% CI)	N	% (95% CI)
Question 10: 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.				
Correct response				
True	105	93.8 (87.5, 97.5)	69	86.3 (76.7, 92.9)
Incorrect response				
False	1	0.9	4	5.0
I don't know	6	5.4	7	8.8
Question 11: Please answer True, False, or I don't know for the following statements:				
11a: 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	101	90.2 (83.1, 95.0)	75	93.8 (86.0, 97.9)
Incorrect response				
False	6	5.4	1	1.3
I don't know	5	4.5	4	5.0

Question	S-5a Internet N=112		S-5b Telephone N=80	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
12b: It is OK for patients to take TIRF medicines for headache pain.				
Correct response				
False	77	68.8 (59.3, 77.2)	59	73.8 (62.7, 83.0)
Incorrect response				
True	13	11.6	4	5.0
I don't know	22	19.6	17	21.3

TABLE 7.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

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=112		S-5b Telephone N=80	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	2	1.8	1	1.3
1 correct response	5	4.5	5	6.3
2 correct responses	37	33.0	24	30.0
3 correct responses	68	60.7	50	62.5
Average number of correct responses	2.5	(2.3, 3.0)	2.5	(2.2, 3.0)

TABLE 8.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

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=112		S-5b Telephone N=80	
	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statements:				
11b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.				
Correct response				
True	56	50.0 (40.4, 59.6)	26	32.5 (22.4, 43.9)
Incorrect response				
False	24	21.4	23	28.8
I don't know	32	28.6	31	38.8
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
12c: TIRF medicines should be taken exactly as prescribed by the doctor.				
Correct response				
True	112	100.0 (96.8, 100.0)	80	100.0 (95.5, 100.0)
Incorrect response				
False	0	0.0	0	0.0
I don't know	0	0.0	0	0.0

Question	S-5a Internet N=112		S-5b Telephone N=80	
	N	% (95% CI)	N	% (95% CI)
Question 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
16b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.				
Correct response				
False	96	85.7 (77.8, 91.6)	62	77.5 (66.8, 86.1)
Incorrect response				
True	5	4.5	5	6.3
I don't know	11	9.8	13	16.3

TABLE 8.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

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=112		S-5b Telephone N=80	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0
1 correct response	11	9.8	16	20.0
2 correct responses	50	44.6	40	50.0
3 correct responses	51	45.5	24	30.0
Average number of correct responses	2.4	(2.1, 3.0)	2.1	(1.8, 3.0)

TABLE 9.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

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=112		S-5b Telephone N=80	
	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statements:				
11c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first				
Correct response				
False	110	98.2 (93.7, 99.8)	76	95.0 (87.7, 98.6)
Incorrect response				
True	0	0.0	1	1.3
I don't know	2	1.8	3	3.8

TABLE 10.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

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=112		S-5b Telephone N=80	
	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statements:				
11d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.				
Correct response				
False	112	100.0 (96.8, 100.0)	80	100.0 (95.5, 100.0)
Incorrect response				
True	0	0.0	0	0.0
I don't know	0	0.0	0	0.0
Question 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
16a: Selling or giving away TIRF medicines is against the law.				
Correct response				
True	110	98.2 (93.7, 99.8)	78	97.5 (91.3, 99.7)
Incorrect response				
False	1	0.9	2	2.5
I don't know	1	0.9	0	0.0

TABLE 10.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

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=112		S-5b Telephone N=80	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0
1 correct response	2	1.8	2	2.5
2 correct responses	110	98.2	78	97.5
Average number of correct responses	2.0	(1.8, 2.0)	2.0	(1.7, 2.0)

TABLE 11.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

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=112		S-5b Telephone N=80	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
12a: TIRF medicines should be stored in a safe place out of the reach of children.				
Correct response				
True	112	100.0 (96.8, 100.0)	80	100.0 (95.5, 100.0)
Incorrect response				
False	0	0.0	0	0.0
I don't know	0	0.0	0	0.0
Question 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
16c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.				
Correct response				
True	107	95.5 (89.9, 98.5)	77	96.3 (89.4, 99.2)
Incorrect response				
False	0	0.0	2	2.5
I don't know	5	4.5	1	1.3
16e: A TIRF medicine can cause an overdose and death in any child who takes it.				
Correct response				
True	102	91.1 (84.2, 95.6)	72	90.0 (81.2, 95.6)
Incorrect response				
False	2	1.8	2	2.5
I don't know	8	7.1	6	7.5

Question	S-5a Internet N=112		S-5b Telephone N=80	
	N	% (95% CI)	N	% (95% CI)
Question 13: 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.	99	88.4 (81.0, 93.7)	72	90.0 (81.2, 95.6)
Incorrect response				
Do nothing.	0	0.0	0	0.0
Wait an hour and see if the person is OK.	3	2.7	3	3.8
I don't know	10	8.9	5	6.3

TABLE 11.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

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=112		S-5b Telephone N=80	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0
2 correct responses	6	5.4	1	1.3
3 correct responses	16	14.3	17	21.3
4 correct responses	90	80.4	62	77.5
Average number of correct responses	3.8	(3.5, 4.0)	3.8	(3.4, 4.0)

TABLE 6.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

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 36):

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

Question	S-6a High School N=39		S-6b Some college N=80		S-6c Bachelor or Master N=66		S-6d Doctoral degree N=7	
	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 statement about the TIRF medicine that was most recently prescribed for you.								
12d: TIRF medicines can cause life-threatening breathing problems that can lead to death.								
Correct response								
True	35	89.7 (75.8, 97.1)	72	90.0 (81.2, 95.6)	59	89.4 (79.4, 95.6)	7	100.0 (59.0, 100.0)
Incorrect response								
False	0	0.0	3	3.8	2	3.0	0	0.0
I don't know	4	10.3	5	6.3	5	7.6	0	0.0

TABLE 7.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

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 36):

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

Question	S-6a High School N=39		S-6b Some college N=80		S-6c Bachelor or Master N=66		S-6d Doctoral degree N=7	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: 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.								
Correct response								
True	32	82.1 (66.5, 92.5)	74	92.5 (84.4, 97.2)	61	92.4 (83.2, 97.5)	7	100.0 (59.0, 100.0)
Incorrect response								
False	1	2.6	3	3.8	1	1.5	0	0.0
I don't know	6	15.4	3	3.8	4	6.1	0	0.0
Question 11: Please answer True, False, or I don't know for the following statements:								
11a: 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	37	94.9 (82.7, 99.4)	72	90.0 (81.2, 95.6)	61	92.4 (83.2, 97.5)	6	85.7 (42.1, 99.6)
Incorrect response								
False	1	2.6	3	3.8	3	4.5	0	0.0
I don't know	1	2.6	5	6.3	2	3.0	1	14.3

Question	S-6a High School N=39		S-6b Some college N=80		S-6c Bachelor or Master N=66		S-6d Doctoral degree N=7	
	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 statement about the TIRF medicine that was most recently prescribed for you.								
12b: It is OK for patients to take TIRF medicines for headache pain.								
Correct response								
False	28	71.8 (55.1, 85.0)	57	71.3 (60.0, 80.8)	46	69.7 (57.1, 80.4)	5	71.4 (29.0, 96.3)
Incorrect response								
True	4	10.3	7	8.8	5	7.6	1	14.3
I don't know	7	17.9	16	20.0	15	22.7	1	14.3

TABLE 7.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

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 36):

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

Demonstrated Understanding	S-6a High School N=39		S-6b Some college N=80		S-6c Bachelor or Master N=66		S-6d Doctoral degree N=7	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	1	1.3	2	3.0	0	0.0
1 correct response	3	7.7	3	3.8	3	4.5	1	14.3
2 correct responses	14	35.9	28	35.0	18	27.3	1	14.3
3 correct responses	22	56.4	48	60.0	43	65.2	5	71.4
Average number of correct responses	2.5	(2.1, 3.0)	2.5	(2.2, 3.0)	2.5	(2.2, 3.0)	2.6	(1.6, 3.0)

TABLE 8.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 36):

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

Question	S-6a High School N=39		S-6b Some college N=80		S-6c Bachelor or Master N=66		S-6d Doctoral degree N=7	
	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 statements:								
11b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.								
Correct response								
True	12	30.8 (17.0, 47.6)	39	48.8 (37.4, 60.2)	27	40.9 (29.0, 53.7)	4	57.1 (18.4, 90.1)
Incorrect response								
False	10	25.6	19	23.8	16	24.2	2	28.6
I don't know	17	43.6	22	27.5	23	34.8	1	14.3
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
12c: TIRF medicines should be taken exactly as prescribed by the doctor.								
Correct response								
True	39	100.0 (91.0, 100.0)	80	100.0 (95.5, 100.0)	66	100.0 (94.6, 100.0)	7	100.0 (59.0, 100.0)
Incorrect response								
False	0	0.0	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-6a High School N=39		S-6b Some college N=80		S-6c Bachelor or Master N=66		S-6d Doctoral degree N=7	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
16b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.								
Correct response								
False	29	74.4 (57.9, 87.0)	70	87.5 (78.2, 93.8)	54	81.8 (70.4, 90.2)	5	71.4 (29.0, 96.3)
Incorrect response								
True	2	5.1	3	3.8	5	7.6	0	0.0
I don't know	8	20.5	7	8.8	7	10.6	2	28.6

TABLE 8.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

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 36):

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

Demonstrated Understanding	S-6a High School N=39		S-6b Some college N=80		S-6c Bachelor or Master N=66		S-6d Doctoral degree N=7	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	8	20.5	8	10.0	9	13.6	2	28.6
2 correct responses	21	53.8	35	43.8	33	50.0	1	14.3
3 correct responses	10	25.6	37	46.3	24	36.4	4	57.1
Average number of correct responses	2.1	(1.7, 3.0)	2.4	(2.1, 3.0)	2.2	(1.9, 3.0)	2.3	(1.3, 3.0)

TABLE 9.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

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 36):

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

Question	S-6a High School N=39		S-6b Some college N=80		S-6c Bachelor or Master N=66		S-6d Doctoral degree N=7	
	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 statements:								
11c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first								
Correct response								
False	36	92.3 (79.1, 98.4)	78	97.5 (91.3, 99.7)	65	98.5 (91.8, 100.0)	7	100.0 (59.0, 100.0)
Incorrect response								
True	1	2.6	0	0.0	0	0.0	0	0.0
I don't know	2	5.1	2	2.5	1	1.5	0	0.0

TABLE 10.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

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 36):

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

Question	S-6a High School N=39		S-6b Some college N=80		S-6c Bachelor or Master N=66		S-6d Doctoral degree N=7	
	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 statements:								
11d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.								
Correct response								
False	39	100.0 (91.0, 100.0)	80	100.0 (95.5, 100.0)	66	100.0 (94.6, 100.0)	7	100.0 (59.0, 100.0)
Incorrect response								
True	0	0.0	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 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
16a: Selling or giving away TIRF medicines is against the law.								
Correct response								
True	39	100.0 (91.0, 100.0)	78	97.5 (91.3, 99.7)	64	97.0 (89.5, 99.6)	7	100.0 (59.0, 100.0)
Incorrect response								
False	0	0.0	2	2.5	1	1.5	0	0.0
I don't know	0	0.0	0	0.0	1	1.5	0	0.0

TABLE 10.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

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 36):

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

Demonstrated Understanding	S-6a High School N=39		S-6b Some college N=80		S-6c Bachelor or Master N=66		S-6d Doctoral degree N=7	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	2	2.5	2	3.0	0	0.0
2 correct responses	39	100.0	78	97.5	64	97.0	7	100.0
Average number of correct responses	2.0	(1.6, 2.0)	2.0	(1.7, 2.0)	2.0	(1.7, 2.0)	2.0	(1.1, 2.0)

TABLE 11.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

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 36):

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

Question	S-6a High School N=39		S-6b Some college N=80		S-6c Bachelor or Master N=66		S-6d Doctoral degree N=7	
	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 statement about the TIRF medicine that was most recently prescribed for you.								
12a: TIRF medicines should be stored in a safe place out of the reach of children.								
Correct response								
True	39	100.0 (91.0, 100.0)	80	100.0 (95.5, 100.0)	66	100.0 (94.6, 100.0)	7	100.0 (59.0, 100.0)
Incorrect response								
False	0	0.0	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 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
16c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.								
Correct response								
True	38	97.4 (86.5, 99.9)	79	98.8 (93.2, 100.0)	61	92.4 (83.2, 97.5)	6	85.7 (42.1, 99.6)

Question	S-6a High School N=39		S-6b Some college N=80		S-6c Bachelor or Master N=66		S-6d Doctoral degree N=7	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Incorrect response								
False	0	0.0	0	0.0	2	3.0	0	0.0
I don't know	1	2.6	1	1.3	3	4.5	1	14.3
16e: A TIRF medicine can cause an overdose and death in any child who takes it.								
Correct response								
True	35	89.7 (75.8, 97.1)	75	93.8 (86.0, 97.9)	57	86.4 (75.7, 93.6)	7	100.0 (59.0, 100.0)
Incorrect response								
False	1	2.6	1	1.3	2	3.0	0	0.0
I don't know	3	7.7	4	5.0	7	10.6	0	0.0
Question 13: 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.	34	87.2 (72.6, 95.7)	74	92.5 (84.4, 97.2)	56	84.8 (73.9, 92.5)	7	100.0 (59.0, 100.0)
Incorrect response								
Do nothing.	0	0.0	0	0.0	0	0.0	0	0.0
Wait an hour and see if the person is OK.	2	5.1	1	1.3	3	4.5	0	0.0
I don't know	3	7.7	5	6.3	7	10.6	0	0.0

TABLE 11.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

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 36):

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

Demonstrated Understanding	S-6a High School N=39		S-6b Some college N=80		S-6c Bachelor or Master N=66		S-6d Doctoral degree N=7	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
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	1	1.3	6	9.1	0	0.0
3 correct responses	10	25.6	10	12.5	12	18.2	1	14.3
4 correct responses	29	74.4	69	86.3	48	72.7	6	85.7
Average number of correct responses	3.7	(3.2, 4.0)	3.9	(3.5, 4.0)	3.6	(3.3, 4.0)	3.9	(2.6, 4.0)

TABLE 6.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

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 5):

- **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=23		S-7b 40 to 49 N=49		S-7c 50 to 59 N=72		S-7d 60 or older N=48	
	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 statement about the TIRF medicine that was most recently prescribed for you.								
12d: TIRF medicines can cause life-threatening breathing problems that can lead to death.								
Correct response								
True	21	91.3 (72.0, 98.9)	44	89.8 (77.8, 96.6)	66	91.7 (82.7, 96.9)	42	87.5 (74.8, 95.3)
Incorrect response								
False	1	4.3	0	0.0	2	2.8	2	4.2
I don't know	1	4.3	5	10.2	4	5.6	4	8.3

TABLE 7.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

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 5):

- **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=23		S-7b 40 to 49 N=49		S-7c 50 to 59 N=72		S-7d 60 or older N=48	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: 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.								
Correct response								
True	21	91.3 (72.0, 98.9)	45	91.8 (80.4, 97.7)	65	90.3 (81.0, 96.0)	43	89.6 (77.3, 96.5)
Incorrect response								
False	1	4.3	2	4.1	2	2.8	0	0.0
I don't know	1	4.3	2	4.1	5	6.9	5	10.4
Question 11: Please answer True, False, or I don't know for the following statements:								
11a: 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	21	91.3 (72.0, 98.9)	47	95.9 (86.0, 99.5)	67	93.1 (84.5, 97.7)	41	85.4 (72.2, 93.9)
Incorrect response								
False	1	4.3	1	2.0	3	4.2	2	4.2
I don't know	1	4.3	1	2.0	2	2.8	5	10.4

Question	S-7a 18 to 39 N=23		S-7b 40 to 49 N=49		S-7c 50 to 59 N=72		S-7d 60 or older N=48	
	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 statement about the TIRF medicine that was most recently prescribed for you.								
12b: It is OK for patients to take TIRF medicines for headache pain.								
Correct response								
False	18	78.3 (56.3, 92.5)	32	65.3 (50.4, 78.3)	55	76.4 (64.9, 85.6)	31	64.6 (49.5, 77.8)
Incorrect response								
True	1	4.3	7	14.3	5	6.9	4	8.3
I don't know	4	17.4	10	20.4	12	16.7	13	27.1

TABLE 7.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

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 5):

- **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=23		S-7b 40 to 49 N=49		S-7c 50 to 59 N=72		S-7d 60 or older N=48	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	1	4.3	0	0.0	1	1.4	1	2.1
1 correct response	0	0.0	3	6.1	3	4.2	4	8.3
2 correct responses	6	26.1	17	34.7	20	27.8	18	37.5
3 correct responses	16	69.6	29	59.2	48	66.7	25	52.1
Average number of correct responses	2.6	(2.1, 3.0)	2.5	(2.2, 3.0)	2.6	(2.3, 3.0)	2.4	(2.0, 3.0)

TABLE 8.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

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 5):

- **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=23		S-7b 40 to 49 N=49		S-7c 50 to 59 N=72		S-7d 60 or older N=48	
	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 statements:								
11b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.								
Correct response								
True	12	52.2 (30.6, 73.2)	18	36.7 (23.4, 51.7)	36	50.0 (38.0, 62.0)	16	33.3 (20.4, 48.4)
Incorrect response								
False	5	21.7	16	32.7	10	13.9	16	33.3
I don't know	6	26.1	15	30.6	26	36.1	16	33.3
Question 12: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
12c: TIRF medicines should be taken exactly as prescribed by the doctor.								
Correct response								
True	23	100.0 (85.2, 100.0)	49	100.0 (92.7, 100.0)	72	100.0 (95.0, 100.0)	48	100.0 (92.6, 100.0)
Incorrect response								
False	0	0.0	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 18 to 39 N=23		S-7b 40 to 49 N=49		S-7c 50 to 59 N=72		S-7d 60 or older N=48	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
16b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.								
Correct response								
False	19	82.6 (61.2, 95.0)	43	87.8 (75.2, 95.4)	62	86.1 (75.9, 93.1)	34	70.8 (55.9, 83.0)
Incorrect response								
True	3	13.0	1	2.0	3	4.2	3	6.3
I don't know	1	4.3	5	10.2	7	9.7	11	22.9

TABLE 8.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

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 5):

- **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=23		S-7b 40 to 49 N=49		S-7c 50 to 59 N=72		S-7d 60 or older N=48	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	3	13.0	4	8.2	8	11.1	12	25.0
2 correct responses	9	39.1	29	59.2	30	41.7	22	45.8
3 correct responses	11	47.8	16	32.7	34	47.2	14	29.2
Average number of correct responses	2.4	(1.8, 3.0)	2.2	(1.9, 3.0)	2.4	(2.1, 3.0)	2.0	(1.7, 3.0)

TABLE 9.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

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 5):

- **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=23		S-7b 40 to 49 N=49		S-7c 50 to 59 N=72		S-7d 60 or older N=48	
	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 statements:								
11c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first								
Correct response								
False	23	100.0 (85.2, 100.0)	47	95.9 (86.0, 99.5)	71	98.6 (92.5, 100.0)	45	93.8 (82.8, 98.7)
Incorrect response								
True	0	0.0	0	0.0	0	0.0	1	2.1
I don't know	0	0.0	2	4.1	1	1.4	2	4.2

TABLE 10.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

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 5):

- **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=23		S-7b 40 to 49 N=49		S-7c 50 to 59 N=72		S-7d 60 or older N=48	
	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 statements:								
11d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.								
Correct response								
False	23	100.0 (85.2, 100.0)	49	100.0 (92.7, 100.0)	72	100.0 (95.0, 100.0)	48	100.0 (92.6, 100.0)
Incorrect response								
True	0	0.0	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 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
16a: Selling or giving away TIRF medicines is against the law.								
Correct response								
True	21	91.3 (72.0, 98.9)	49	100.0 (92.7, 100.0)	70	97.2 (90.3, 99.7)	48	100.0 (92.6, 100.0)
Incorrect response								
False	1	4.3	0	0.0	2	2.8	0	0.0
I don't know	1	4.3	0	0.0	0	0.0	0	0.0

TABLE 10.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

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 5):

- **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=23		S-7b 40 to 49 N=49		S-7c 50 to 59 N=72		S-7d 60 or older N=48	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	2	8.7	0	0.0	2	2.8	0	0.0
2 correct responses	21	91.3	49	100.0	70	97.2	48	100.0
Average number of correct responses	1.9	(1.4, 2.0)	2.0	(1.7, 2.0)	2.0	(1.7, 2.0)	2.0	(1.7, 2.0)

TABLE 11.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

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 5):

- **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=23		S-7b 40 to 49 N=49		S-7c 50 to 59 N=72		S-7d 60 or older N=48	
	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 statement about the TIRF medicine that was most recently prescribed for you.								
12a: TIRF medicines should be stored in a safe place out of the reach of children.								
Correct response								
True	23	100.0 (85.2, 100.0)	49	100.0 (92.7, 100.0)	72	100.0 (95.0, 100.0)	48	100.0 (92.6, 100.0)
Incorrect response								
False	0	0.0	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 18 to 39 N=23		S-7b 40 to 49 N=49		S-7c 50 to 59 N=72		S-7d 60 or older N=48	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 16: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
16c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.								
Correct response								
True	23	100.0 (85.2, 100.0)	48	98.0 (89.1, 99.9)	67	93.1 (84.5, 97.7)	46	95.8 (85.7, 99.5)
Incorrect response								
False	0	0.0	0	0.0	1	1.4	1	2.1
I don't know	0	0.0	1	2.0	4	5.6	1	2.1
16e: A TIRF medicine can cause an overdose and death in any child who takes it.								
Correct response								
True	21	91.3 (72.0, 98.9)	47	95.9 (86.0, 99.5)	64	88.9 (79.3, 95.1)	42	87.5 (74.8, 95.3)
Incorrect response								
False	0	0.0	1	2.0	2	2.8	1	2.1
I don't know	2	8.7	1	2.0	6	8.3	5	10.4

Question	S-7a 18 to 39 N=23		S-7b 40 to 49 N=49		S-7c 50 to 59 N=72		S-7d 60 or older N=48	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: 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.	21	91.3 (72.0, 98.9)	46	93.9 (83.1, 98.7)	65	90.3 (81.0, 96.0)	39	81.3 (67.4, 91.1)
Incorrect response								
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	4.3	1	2.0	3	4.2	1	2.1
I don't know	1	4.3	2	4.1	4	5.6	8	16.7

TABLE 11.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

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 5):

- **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=23		S-7b 40 to 49 N=49		S-7c 50 to 59 N=72		S-7d 60 or older N=48	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
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	1	4.3	0	0.0	3	4.2	3	6.3
3 correct responses	2	8.7	6	12.2	14	19.4	11	22.9
4 correct responses	20	87.0	43	87.8	55	76.4	34	70.8
Average number of correct responses	3.8	(3.2, 4.0)	3.9	(3.4, 4.0)	3.7	(3.3, 4.0)	3.6	(3.2, 4.0)

11.4.2 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	Final Wave 1, Version 1.0
Product Name:	Transmucosal Immediate Release Fentanyl
Sponsor:	**TIRF REMS Industry Group (TRIG) of Companies:** Archimedes Pharma US, Inc. Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Insys Therapeutics Meda Pharmaceuticals Mallinckrodt (the Pharmaceuticals Business of Covidien) Par Pharmaceutical, Inc. ProStrakan, Inc.
Date:	14 December 2012

Confidentiality Statement

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LIST OF ABBREVIATIONS

CSP	Closed System Pharmacy
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
KAB	Knowledge, Attitudes, and Behavior
PI	Prescribing Information
REMS	Risk Evaluation and Mitigation Strategy
SAP	Statistical Analysis Plan
SERP	Safety Event Reporting Plan
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

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 Archimedes Pharma United States (US) Inc., Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.), Insys Therapeutics, Meda Pharmaceuticals, Mallinckrodt (the Pharmaceuticals Business of Covidien), Par Pharmaceutical, Inc., and ProStrakan, Inc. At the time of protocol development for the Knowledge, Attitude, and Behavior (KAB) surveys, Sandoz was also a member of the TRIG; however Sandoz terminated their involvement in the TIRF REMS Access program, effective 15 September 2012.

The Food and Drug Administration (FDA) has determined that a class-wide 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 (PI) of each product. The protocol describes the administration of these surveys 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.

Results from the surveys will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

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 constructed 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 pharmacists who were enrolled in the TIRF REMS Access program as of 15 August 2012. A target sample of 300 pharmacists who dispense TIRF products and were known to have received the REMS educational materials were surveyed in

this first KAB survey conducted from 24 September 2012 to 01 November 2012. The size of the sample was determined based on both practical and statistical considerations.

Subject recruitment was 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' immediate family members who had ever worked for the 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 first wave of the TIRF survey will not be eligible to participate in subsequent survey waves.

Potential subjects were recruited via a letter sent through the United States Postal Service, faxed, and additionally outbound calls were made (see Section 5.1.1 for more detail).

The required number of completed surveys from the initial mailing was not achieved as expected within approximately 10 days after the first mailing. A second mailing was sent to non-respondents from the original sample with subsequent fax, email, or telephone follow-up to maximize participation. These efforts did not result in the required number of surveys within approximately 21 days, and an additional sample of potential subjects was randomly selected.

Pharmacists were given the option of taking the survey by telephone via the Survey Coordinating Center 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**
6	Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.	
6a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	***True***
6b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	***True***
6c	TIRF medicines may be used to treat opioid non-tolerant patients.	***False***
6d	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**
8	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.	
8a	Acute or postoperative pain	***No***
8b	Headache or migraine pain	***No***
8c	Dental pain	***No***
8d	Breakthrough pain from cancer	***Yes***

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**
6	Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.	
6e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	***True***
7	Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.	
7a	A personal history of psychiatric illness	***Yes***
7b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	***Yes***
9	Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.	
9a	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**
9	Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.	
9b	TIRF medicines are interchangeable with each other regardless of route of administration.	**False**
9c	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**
9d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**True**

3.3 Additional Questions

The survey also contained questions about the requirements of the TIRF REMS Access program and receipt and understanding of the TIRF educational materials. The following question about behaviors was asked after the key risk message questions:

Question: How frequently do you perform the following activities when dispensing TIRF medicines?
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

4. STATISTICAL METHODS

4.1 Study Population

4.1.1 Primary Analysis Population

According to the prospective Statistical Analysis Plan (SAP), 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 Question 3 (work at a pharmacy that is enrolled in the TIRF REMs Access program), and ***No*** to Question 2 (participated in past survey; not applicable for Wave 1) 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-populations of Interest

The following subgroup analyses were conducted if the subgroup included at least 20 respondents.

- Subpopulation S-1:

a) Pharmacists who received and read the TIRF medicine educational materials (***Yes*** for Question 17 [Full Prescribing Information], or ***Yes*** for Question 19 [Medication Guide]).

b) Pharmacists who did not read the full prescribing information for the TIRF medicine educational materials (***No or I don't know*** for Question 17 [Full Prescribing Information], or ***No or I don't know*** for Question 19 [Medication Guide]).

- Subpopulation S-2: Time to complete survey-Internet (***<10 min, 10 to <20 min, or ≥20 min***);
- Sub-population S-3: Time to complete survey-Telephone (***<10 min, 10 to <20 min, or ≥20 min***);
- Subpopulation S-4: Modality to complete survey (***Internet or Telephone***)
- Subpopulation S-5: Time practicing as a pharmacist (***less than 3 years, 3 to 5 years, 6 to 15 years, or more than 15 years*** for Question 26)
- Subpopulation S-6: Number of times per month dispensing TIRF medicines within the last 6 months (***None, 1-2 times, 3-5 times, or more than 5 times a month*** for Question 23).

4.1.2.2 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/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).

4.1.2.3 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.

4.1.3 Pharmacist Report of Adverse Event, Product Complaint, or Medical Information Request During Survey

A pharmacist may have reported an adverse event or other safety event experienced by their patients while taking a TIRF product either in free text fields in the survey or while in conversation with the Survey Coordinating Center. If the event was mentioned to a Survey Coordinating Center Associate, the Associate documented the safety event and the pharmacist's contact information if provided. The pharmacist was also informed that a representative from the appropriate TIRF medicine manufacturer might contact them to obtain additional information about the safety event. The Internet surveys were monitored for any comments recorded in the free text fields. Information on all reports (Internet or Telephone) that constituted an adverse event or other safety event was forwarded to the appropriate TIRF medicine manufacturer for processing within 1 business day of awareness of the event as outlined in the Safety Event Reporting Plan (SERP).

5. RESULTS

Results of the pharmacist responses to questions in the KAB survey are summarized in this section.

5.1 Survey Participants

5.1.1 Survey Participant Administration Results

A total of 7236 pharmacists were invited to participate in this survey (Table 1). Of those invited to participate, 6286 were outpatient pharmacists, 650 were inpatient pharmacists, and 300 were pharmacists practicing in Closed System Pharmacies (CSPs). In order to increase the total overall response, 98 out bound calls were made from 09 October 2012 to 11 October 2012. Reminder invitations were sent to potential participants to reduce volunteer bias. Some pharmacists received more than 1 reminder.

In all, a total of 302 pharmacists met eligibility criteria and completed the survey. Of these 302 pharmacists, 286 (94.7%) completed the survey online, and 16 (5.3%) completed it by telephone (Table 3).

From the 302 respondents, 304 surveys were collected. It was identified that 2 respondents completed the survey twice. Only the first completed survey was included in the analysis for each respondent. Of the 302 pharmacists who completed the survey, 6 were CSP pharmacists, 16 were inpatient pharmacists, and 280 were outpatient pharmacists (Table 14).

Table 1. Survey Participant Administration Results

Summary Statistic	Screened Pharmacists N=348[1]	
	All Respondents	
	N	%
Number of invitations issued to pharmacists	7236	
Number of reminder letters issued to pharmacists	11607	
Number of pharmacists screened for participation	348[1]	
Number of pharmacists eligible for participation	302	
Number of pharmacists completing the survey	302	86.8
By telephone	16	4.6
By internet	286	82.2

[1] This is the denominator for the percentages in this table (N=348).

As shown in Table 2, a total of 348 pharmacists agreed to participate in this survey and 304 of these pharmacists worked in pharmacies that were enrolled in the TIRF REMS. Of the 348 total respondents, 44 were ineligible to participate in the survey because they worked in pharmacies that were not enrolled or they did not know whether their pharmacy was enrolled in the TIRF REMS. Of the 304 respondents who reported that their pharmacies were enrolled in the TIRF REMS Access program, 1 respondent was ineligible for the survey because the respondent, or an immediate family member, had worked for a TRIG company in the past, and 1 respondent did not know whether he/she or an immediate family member had worked for a TRIG company, UBC, Specialty Care Solutions, RelayHealth, or FDA in the past.

Table 2. Survey Participant Screening Results

Question	All Respondents N=348		Eligible Completed Pharmacists N=302	
	n	%	n	%
Question 1: Do you agree to participate in this survey?				
Yes	348	100.0	302	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	4	1.1	4	1.3
No	338	97.1	293	97.0
I don't know	6	1.7	5	1.7
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	304	87.4	302	100.0
No[1]	15	4.3		
I don't know[1]	29	8.3		
Question not asked [2]	0	0.0		

(continued)

Table 2. Survey Participant Screening Results

Question	All Respondents N=348		Eligible Completed Pharmacists N=302	
	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]	1	0.3		
Archimedes Pharma US Inc.[1]	1	0.3		
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)[1]	1	0.3		
Endo Pharmaceuticals Inc.[1]	1	0.3		
Insys Therapeutics[1]	1	0.3		
McKesson Specialty Care Solutions[1]	1	0.3		
Mallinckrodt (the Pharmaceuticals Business of Covidien)[1]	1	0.3		
Meda Pharmaceuticals[1]	1	0.3		
Par Pharmaceutical, Inc.[1]	1	0.3		
ProStrakan, Inc.[1]	1	0.3		
Sandoz Inc.[1]	1	0.3		
Teva Pharmaceuticals, Ltd.[1]	1	0.3		
RelayHealth[1]	1	0.3		
United BioSource Corporation[1]	0	0.0		
FDA[1]	0	0.0		
None of these apply[4]	302	86.8	302	100.0
I don't know[1]	1	0.3		
Prefer not to answer[1]	0	0.0		
Question not asked[2]	44	12.6		

[1] Ineligible to participate in the survey.

[2] Question not asked due to a previous question elimination.

[3] More than 1 response can be selected, so percentages may not sum to 100%.

[4] Ineligible if selected in addition to another response.

Those taking the survey online took an average of 12.2 minutes to complete it, while those taking it by telephone took an average of 16.6 minutes.

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

Summary Statistic	Telephone	Internet	Total [1]
N	16	286	302
Mean (Standard Deviation)	16.6 (4.34)	12.2 (6.54)	12.4 (6.51)
Minimum	11	4	4
Median	15.9	10.7	10.9
Maximum	28	51	51
Category			
0 – <5 Minutes	0	2	2
5 – <10 Minutes	0	130	130
10 – <15 Minutes	8	87	95
15 – <20 Minutes	6	43	49
20 – <25 Minutes	1	12	13
25 – <30 Minutes	1	6	7
30 Minutes or More	0	6	6

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

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 (66.9%). Respondents from the South, Northeast, and Midwest reflected 34.4%, 26.5%, and 21.5% of total respondents, respectively, while respondents from the Western region of the US composed 17.2% of total respondents. The proportion of respondents who completed the survey within each geographic region was similar to the overall proportion of pharmacists (37,480 pharmacists enrolled in the TIRF REMS Access program as of 15 August 2012) in each geographic region (Table 4). Almost half (48.0%) had been a practicing pharmacist for more than 15 years.

The majority of pharmacists (82.1%) functioned as the pharmacist in charge for the TIRF REMS Access program where they worked. Most pharmacists (74.2%) had dispensed a TIRF medicine zero to 2 times per month within the past 6 months, and the most frequently dispensed TIRF medicine within the 6 months prior to taking the survey was Actiq or generic Actiq (76.7%). Four pharmacists indicated that they dispensed Onsolis during the 6 months prior to taking the survey, which would be after March 23, 2012. However, Onsolis was not available to any pharmacy at that time. The last Onsolis provided to patients was in May 2011.

Table 4. Demographic Characteristics of Eligible Pharmacists

Question	Eligible Completed Pharmacists N=302[1]	
	n	%
Question 25: What is your gender?		
Male	202	66.9
Female	95	31.5
Prefer not to answer	5	1.7
Question 26: In total, how many years have you been a practicing pharmacist		
Less than 3 years	25	8.3
3-5 years	41	13.6
6-10 years	51	16.9
11-15 years	37	12.3
More than 15 years	145	48.0
Prefer not to answer	3	1.0

Question 27: In which state do you practice?[2]				
Geographic Region[1]	**Eligible and Complete Respondents N=302**		**Enrolled in TIRF REMS Access Program on 15AUG2012 N=37,480**	
	N	**%**	**N**	**%**
Northeast	80	26.5	7362	21.0
Midwest	65	21.5	7874	19.6
South	104	34.4	14574	38.9
West	52	17.2	7516	20.1
Other	0	0.0	154	0.4
Prefer not to answer	1	0.3		

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

[2] According to the 2001 Geographic Area Regions set by the US Census Bureau, 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. Other includes 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=302[1]	
	n	%
Question 22: Are you the Pharmacist in Charge for the TIRF REMS Access program where you work?		
Yes	248	82.1
No	47	15.6
I don't know	7	2.3
Question 23: On average, how many times per month have you dispensed the TIRF medicines within the last 6 months		
None	122	40.4
1-2 times per month	102	33.8
3-5 times per month	29	9.6
More than 5 times per month	23	7.6
I don't remember	26	8.6
Question 24: Please select the TIRF medicines that you have dispensed within the last 6 months (select all that apply):[2]		
Abstral®	11	6.1
Actiq® or generic Actiq®	138	76.7
Fentora®	70	38.9
Lazanda®	9	5.0
Onsolis®	4	2.2
Subsys®	18	10.0
N/A (answered None to Question 23)	122	

[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. N/A =

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). Most respondents reported they had received or had access to the Full Prescribing Information and the Medication Guide (97.7% and 97.0%, respectively). Of those with access to these materials, 75.3% and 82.9%, 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=302[1]	
	n	%
Question 16: Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine that you dispense?		
Yes	295	97.7
No	1	0.3
I don't know	6	2.0
Question 17: Did you read the Full Prescribing Information for the TIRF medicine that you dispense?[2,]		
Yes	222	75.3
No	59	20.0
I don't know	14	4.7
N/A (answered ***No*** or ***I don't know*** to Question 16)	7	
Question 18: Did you receive or do you have access to the Medication Guide for the TIRF medicine that you dispense?		
Yes	293	97.0
No	4	1.3
I don't know	5	1.7

(continued)

Table 6. Responses to Questions About TIRF Medicines Educational Materials

Question 19: Did you read the Medication Guide for the TIRF medicine that you dispense?[2]		
Yes	243	82.9
No	39	13.3
I don't know	11	3.8
N/A (answered ***No*** or ***I don't know*** to Question 18)	9	
Question 20: Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?		
Yes[3]	15	5.0
No	266	88.1
I don't know	21	7.0

[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 are presented in Listing 1.

There were 15 respondents who typed a response into the free text field for Question 21. These responses are categorized in Table 7 (see verbatim responses shown in Appendix B, Listing 1). Six of the responses questions categorized as "generalized response" (1.9% were primarily statements that respondents had no questions at the time of the survey or they meant to answer 'no' on a previous question.

Table 7. Categorized Responses To Question 21 (Questions About the Information in the Full Prescribing Information or Medication Guide)

Response (Categorized Type) [2]	Eligible Completed Pharmacists N=302 [1]	
	n [3]	%
Abuse monitoring	1	0.3
Dosage, Side Effects	1	0.3
Medication Guide distribution	1	0.3
Medication Guide distribution/format	1	0.3
Prescribing Information request	1	0.3

(continued)

Table 7. Categorized Responses To Question 21 (Questions About the Information in the Full Prescribing Information or Medication Guide)

Response (Categorized Type) [2]	Eligible Completed Pharmacists N=302 [1]	
	n [3]	%
REMS process	2	0.7
General responses (specific questions not asked)	6	1.9

[1] Number of eligible pharmacists completing the survey (See Table 1).
[2] Categorization scheme of the verbatim responses is shown in Appendix B, Listing 1.
[3] Each category is only counted once per pharmacist.

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 subgroup 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 in patients.

Analysis of responses to components of Question 6 for Key Risk Message 1 showed that a high percentage of pharmacists knew that TIRF medicines are contraindicated in opioid non-tolerant patients (86.1%) and that death has occurred in opioid non-tolerant patients treated with some fentanyl products (92.1%). Most pharmacists were aware that dose titration for patients starting a TIRF medicine must begin with the lowest available dose for that product (78.5%) and that TIRF medicines may not be used to treat opioid non-tolerant patients (78.5%), (Table 8). Evidence of understanding of this key risk information is further supported by the average number of 3.4 out of a possible 4 correct responses.

Table 8. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible Completed Pharmacists N=302[1]	
	n	% (95% CI)[3]
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.		
6a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True [2]	260	86.1 (81.7, 89.8)
False	24	7.9
I don't know	18	6.0
6b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True [2]	278	92.1 (88.4, 94.8)
False	5	1.7
I don't know	19	6.3
6c: TIRF medicines may be used in opioid non-tolerant patients.		
True	48	15.9
False[2]	237	78.5 (73.4, 83.0)
I don't know	17	5.6
6d: 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	78.5 (73.4, 83.0)
False	46	15.2
I don't know	19	6.3

(continued)

Table 8. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible Completed Pharmacists N=302[1]	
	n	% (95% CI)[3]
Secondary Analysis: Demonstrated Understanding		
0 correct responses	2	0.7
1 correct response	13	4.3
2 correct responses	34	11.3
3 correct responses	81	26.8
4 correct responses	172	57.0
Average number of correct responses	3.4	(3.2, 4.0)[4]

[1] Number of eligible pharmacists completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or item 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 8 for Key Risk Message 2 indicate that most pharmacists were aware TIRF medicines are prescribed for adult opioid-tolerant patients with breakthrough pain from cancer (83.4%) and not for patients with acute or postoperative pain (78.1%), headache or migraine pain (89.1%),or dental pain (94.7%), (Table 9). Evidence of understanding of this key risk information is further supported by an average number of 3.5 out of a possible 4 correct responses.

Table 9. 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=302[1]	
	n	% (95% CI)[3]
Question 8: 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.		
8a: Acute or postoperative pain		
Yes	52	17.2
No[2]	236	78.1 (73.1, 82.7)
I don't know	14	4.6
8b: Headache or migraine pain		
Yes	12	4.0
No[2]	269	89.1 (85.0, 92.4)
I don't know	21	7.0
8c: Dental pain		
Yes	6	2.0
No[2]	286	94.7 (91.5, 96.9)
I don't know	10	3.3
8d: Breakthrough pain from cancer		
Yes [2]	252	83.4 (78.8, 87.5)
No	46	15.2
I don't know	4	1.3

(continued)

Table 9. 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=302[1]	
	n	% (95% CI)[3]
Secondary Analysis: Demonstrated Understanding		
0 correct responses	2	0.7
1 correct response	11	3.6
2 correct responses	19	6.3
3 correct responses	86	28.5
4 correct responses	184	60.9
Average number of correct responses	3.5	(3.3, 4.0)[4]

[1] Number of eligible pharmacists completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or item 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 6, 7, and 9 for Key Risk Message 3 showed that a high percentage of pharmacists were aware that it is important to monitor for signs of abuse and addiction in patients who take TIRF medicines (97.7%); 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 (99.7%); and TIRF medicines can be abused in a manner similar to other opioid agonists (90.4%). More than half of pharmacists were aware that a personal history of psychiatric illness is a risk factor for opioid abuse (66.6%), (Table 10). Evidence of understanding of this key risk information is further supported by an average number of 3.5 out of a possible 4 correct responses.

Table 10. 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=302[1]	
	n	% (95% CI) [3]
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.		
6e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True [2]	295	97.7 (95.3, 99.1)
False	5	1.7
I don't know	2	0.7
Question 7: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.		
7a: A personal history of psychiatric illness		
Yes [2]	201	66.6 (60.9, 71.9)
No	62	20.5
I don't know	39	12.9
7b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes [2]	301	99.7 (98.2, 100.0)
No	0	0.0
I don't know	1	0.3
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.		
9a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True[2]	273	90.4 (86.5, 93.5)
False	19	6.3
I don't know	10	3.3

(continued)

Table 10. 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=302[1]	
	n	% (95% CI)[3]
Secondary Analysis: Demonstrated Understanding		
0 correct responses	1	0.3
1 correct response	0	0.0
2 correct responses	13	4.3
3 correct responses	108	35.8
4 correct responses	180	59.6
Average number of correct responses	3.5	(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 item 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 9 for Key Risk Message 4 showed that a high percentage of pharmacists understood TIRF medicines are not interchangeable with each other regardless of the route of administration (95.0%); the conversion of 1 TIRF medicine to another may result in a fatal overdose (92.7%); and dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (92.4%), (Table 11). Evidence of understanding of this key risk information is further supported by an average number of 2.8 out of a possible 3 correct responses.

Table 11. 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=302 [1]	
	n	% (95% CI) [3]
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.		
9b: TIRF medicines are interchangeable with each other regardless of route of administration.		
True	9	3.0
False[2]	287	95.0 (91.9, 97.2)
I don't know	6	2.0
9c: 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]	280	92.7 (89.2, 95.4)
False	10	3.3
I don't know	12	4.0
9d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True[2]	279	92.4 (88.8, 95.1)
False	10	3.3
I don't know	13	4.3
Secondary Analysis: Demonstrated Understanding		
0 correct responses	3	1.0
1 correct response	5	1.7
2 correct responses	41	13.6
3 correct responses	253	83.8
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 item 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 12 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 confirmed the pharmacists' understanding of the safety issues and the risks associated with taking TIRF medicines.

A high percentage of pharmacists correctly indicated that TIRF medicines may not be sold, loaned, or transferred to another pharmacy (86.8%); pharmacy staff who dispense TIRF medicines must be educated on the requirements of the TIRF REMS Access program (92.7%); and that TIRF medicines with the same route of administration cannot be substituted with each other (95.7%). The majority of inpatient pharmacists correctly indicated that it is not OK to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for home use (87.5%; Table 13).

Despite the high proportion of pharmacists responding correctly to the questions around Key Risk Message 1 (i.e., that patients must be opioid tolerant), only 12.6% of pharmacists correctly indicated that patients considered opioid tolerant are those who are taking regular opioid therapy for 1 week or longer. Additionally, 15.6% correctly indicated that patients not currently taking opioid therapy but who have no known intolerance or hypersensitivity to fentanyl are not considered opioid tolerant. In contrast a high percentage (80.1%) correctly indicated patients not currently taking opioid therapy but who had taken opioid therapy before are not considered opioid tolerant.

Because the results for the 2 components of Question 5 are discrepant from the other pharmacist results around opioid tolerance, it is possible that these results reflect a misunderstanding of the question rather than a lack of understanding of the important safety information. Additional research will be conducted to explore pharmacists' interpretation and understanding of all 3 components of Question 5. The outcome of the research will be included in the next assessment report, and action proposed, if appropriate.

Table 12. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Pharmacists N=302[1]	
	n	%
Question 5: Please answer "True," "False," or "I don't know" for each of the following. According to the labeling, patients considered opioid-tolerant are those:		
5a: Who are taking regular opioid therapy for underlying persistent cancer pain for one week or longer.		
True [2]	38	12.6
False	255	84.4
I don't know	9	3.0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before.		
True	46	15.2
False[2]	242	80.1
I don't know	14	4.6
5c: Who are not currently taking opioid therapy, but with no known intolerance or hypersensitivity to the drug fentanyl		
True	242	80.1
False [2]	47	15.6
I don't know	13	4.3
Question 7: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.		
7c: A family history of asthma		
Yes	26	8.6
No[2]	251	83.1
I don't know	25	8.3

(continued)

Table 12. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Pharmacists N=302[1]	
	n	%
Question 8: 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.		
8e: Chronic non-cancer pain		
Yes	194	64.2
No[2]	90	29.8
I don't know	18	6.0
Question 11: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.		
11a: TIRF medicines may be sold, loaned, or transferred to another pharmacy.		
True	14	4.6
False[2]	262	86.8
I don't know	26	8.6
11b: All pharmacy staff that dispenses TIRF medicines must be educated on the requirements of the TIRF REMS Access program.		
True [2]	280	92.7
False	12	4.0
I don't know	10	3.3
11c: 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	5	1.7
False[2]	289	95.7
I don't know	8	2.6

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

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

Table 13. Responses to Additional Questions About the Safe Use of TIRF Medicines: Question asked of Inpatient Pharmacists, Only

Question	Eligible Completed Inpatient Pharmacists N=16[1]	
	n	%
Question 15: 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	12.5
False[2]	14	87.5
I don't know	0	0.0

[1] Question asked of inpatient pharmacists only.

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

[3] This question is presented only to a subgroup 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 14).

More than half of the pharmacists indicated they always give patients (or their caregivers) the Medication Guide for TIRF medicine (90.1%), instruct the patient (or their caregivers) not to share TIRF medicines (66.9%), counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal (62.9%), instruct patients (or their caregivers) to keep TIRF medicines out of reach of children (68.9%), and instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines (57.0%). Almost half (48.3%) of the pharmacists always ask their patients (or their caregivers) about the presence of children in the home, with 22.5% asking only with the first prescription.

Table 14. Responses to All Questions About Activities When Dispensing TIRF Medicines

Question	Eligible Completed Pharmacists N=302 [1]	
	n	%
Question 10: 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."		
10a: Ask patients (or their caregivers) about the presence of children in the home.		
Always	146	48.3
Only with the first prescription	68	22.5
Sometimes	54	17.9
Never	28	9.3
I don't know	6	2.0
10b: Instruct patients (or their caregivers) not to share TIRF medicines with anyone else.		
Always	202	66.9
Only with the first prescription	54	17.9
Sometimes	26	8.6
Never	15	5.0
I don't know	5	1.7
10c: Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal.		
Always	190	62.9
Only with the first prescription	63	20.9
Sometimes	29	9.6
Never	13	4.3
I don't know	7	2.3

(continued)

Table 14. Responses to All Questions About Activities When Dispensing TIRF Medicines

Question	Eligible Completed Pharmacists N=302 [1]	
	n	%
10d: Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure.		
Always	208	68.9
Only with the first prescription	56	18.5
Sometimes	21	7.0
Never	12	4.0
I don't know	5	1.7
10e: Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines.		
Always	172	57.0
Only with the first prescription	76	25.2
Sometimes	34	11.3
Never	13	4.3
I don't know	7	2.3
10f: Give patients (or their caregivers) the Medication Guide for their TIRF medicine.		
Always	272	90.1
Only with the first prescription	17	5.6
Sometimes	5	1.7
Never	3	1.0
I don't know	5	1.7

[1] Number of eligible pharmacists completing the survey (See Table 1).
[2] This question is presented only to a subgroup of pharmacists. Percentages are based on the number of pharmacists to whom this question was presented.

Specific pharmacy types (inpatient, outpatient, and closed system pharmacy [CSP] pharmacies) were each asked a single different question regarding pharmacy systems and processes. Question 12 was presented only to pharmacy respondents from inpatient pharmacies (N=16) as identified through the access code entered by the respondent (Table 15). Fifty percent (50.0%) of these respondents reported their pharmacy has processes to ensure compliance with the TIRF REMS Access program requirements.

Table 15. Responses to All Questions About Activities When Dispensing TIRF Medicines: Asked of Inpatient Pharmacies, Only

Question	Eligible Completed Inpatient Pharmacists N=16 [1]	
	n	%
Question 12: 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	8	50.0
No	6	37.5
I don't know	2	12.5

[1] Number of eligible inpatient pharmacists completing the survey.
[2] This question is presented only to a subgroup of pharmacists. Percentages are based on the number of pharmacists to whom this question was presented.

Question 13 was presented only to pharmacy respondents from outpatient pharmacies (N=280) as identified through the access code entered by the respondent. This sub-population did not include respondents from CSPs (Table 16). The majority (83.9%) of these respondents reported their pharmacy processes prescriptions for TIRF medicines through their pharmacy management system.

Table 16. Responses to All Questions About Activities When Dispensing TIRF Medicines: Outpatient Pharmacists, Only

Question	Eligible Completed Outpatient Pharmacists N=280 [1]	
	n	%
Question 13: 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	235	83.9
No	7	2.5
I don't know	38	13.6

[1] Number of eligible outpatient pharmacists completing the survey.
[2] This question is presented only to a subgroup of pharmacists. Percentages are based on the number of pharmacists to whom this question was presented.

Question 14 was presented only to pharmacy respondents from CSPs (N=6) as identified through the access code entered by the respondent (Table 17). The majority (83.3%) of CSP respondents reported their pharmacy processes all prescriptions for TIRF medicines through the TIRF REMS Access Call Center.

Table 17. Responses to All Questions About Activities When Dispensing TIRF Medicines: Closed System Pharmacy Outpatient Pharmacists, Only

Question	Eligible Completed CSP Pharmacists N=6 [1]	
	n	%
Question 14: 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	5	83.3
No	0	0.0
I don't know	1	16.7

[1] Number of eligible CSP outpatient pharmacists completing the survey.
[2] This question is presented only to a subgroup of pharmacists. Percentages are based on the number of pharmacists to whom this question was presented.

5.2.3 Analyses of Subpopulations

To further assess pharmacist understanding of key risk messages, subgroup analyses as described in Section 4.1.2 were conducted. All results are similar to the results in the primary analysis population, and no trends are evident. The full set of subgroup 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=348), no pharmacists reported an adverse event, product complaint, or requested medical information associated with the use of TIRF medicines during phone completions of this survey. Five reports of adverse events, product complaints, and/or medical information requests were reported in the free text fields of surveys completed online by pharmacists (Table 18; Appendix B: Listing 2). Adverse event, product complaint, or medical information request reports were categorized as described in Table 19.

Table 18. Respondent Report of Adverse Event, Product Complaint, or Medical Information Request During Survey

Question	All Respondents N=348[1]	
	n	%
Respondent spontaneously reported an adverse event, product complaint, or medical information request during the course of this survey.		
Yes [2]	5	1.4
No	343	98.6

[1] All respondents who took the survey regardless of eligibility.
[2] Verbatim text of adverse events, product complaints, or medical information requests is given in Appendix B, Listing 2.

Table 19. Categorized Reported Adverse Events, Product Complaints, or Medical Information Request

Response (Categorized Type)[2]	All Respondents N=348[1]	
	n [3]	%
Abuse monitoring	1	0.3
Dosage, Side Effects	1	0.3
REMS process	1	0.3
Prescribing Information request	1	0.3
Medication Guide distribution/format	1	0.3

[1] All respondents who took the survey regardless of eligibility.
[2] Categorization scheme of the verbatim responses is shown in Appendix B, Listing 2.
[3] Each category is only counted once per pharmacist.

5.4 Discussion, Conclusions, and Recommendations

The specific goals of the TIRF medicines pharmacist KAB survey were to assess pharmacist understanding of the risks associated with TIRF medicine use, of the specific indications for treatment with TIRF medicines, and that TIRF medicines are contraindicated in opioid non-tolerant patients.

The survey invited 7236 pharmacists (based on TIRF REMS enrollment records), of whom 302 met the inclusion criteria for the survey. The majority of respondents were male (66.9%). Respondents from the South, Northeast, and Midwest reflected 34.4%, 26.5%, and 21.5% of total respondents, respectively, while respondents from the Western region of the US

composed 17.2%, of the total survey population. The proportion of eligible completed pharmacists within each geographic region was similar to the overall proportion of pharmacists (37,480 pharmacists enrolled in the TIRF REMS Access program as of 10 August 2012) in each geographic region. Almost half (48.0%) of eligible respondents who completed the survey had been a practicing pharmacist for more than 15 years. The majority of respondents (82.1%) self-identified themselves as the pharmacist in charge for the TIRF REMS Access program where they worked. Most respondents received or had access to the Full Prescribing Information and the Medication Guide (97.7% and 97.0%, respectively). Of those with access to these materials, 75.3% and 82.9%, claimed to have read the Full Prescribing Information and the Medication Guide, respectively.

There were 4 key risk messages included in the survey. Pharmacists demonstrated a high level of understanding of each key risk message. There was a correct response rate of greater than 78% for all components of Key Risk Messages 1, 2, and 4, with the exception of a correct response rate of 66% for Key Risk Message 3, which included questions that assessed the pharmacist's understanding that a personal history of psychiatric illness is a risk factor for opioid abuse.

Analysis of responses to components of Question 6 for Key Risk Message 1 (TIRF medicines are contraindicated in opioid non-tolerant patients) showed that a high percentage of pharmacists knew that TIRF medicines are contraindicated in opioid non-tolerant patients (86.1%) and that death has occurred in opioid non-tolerant patients treated with some fentanyl products (92.1%). Most pharmacists were aware that dose titration for patients starting a TIRF medicine must begin with the lowest available dose for that product (78.5%) and that TIRF medicines may not be used to treat opioid non-tolerant patients (78.5%).

Responses to components of Question 8 for Key Risk Message 2 indicate that most pharmacists were aware TIRF medicines are prescribed for adult opioid-tolerant patients with breakthrough pain from cancer (83.4%) and not for patients with acute or postoperative pain (78.1%), headache or migraine pain (89.1%), or dental pain (94.7%).

Responses to components of Questions 6, 7, and 9 for Key Risk Message 3 showed that a high percentage of pharmacists were aware that it is important to monitor for signs of abuse and addiction in patients who take TIRF medicines (97.7%); 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 (99.7%); and TIRF medicines can be abused in a manner similar to other opioid agonists (90.4%).

Responses to components of Question 9 for Key Risk Message 4 showed that a high percentage of pharmacists understood TIRF medicines are not interchangeable with each other regardless of the route of administration (95.0%); the conversion of 1 TIRF medicine to another may result in a fatal overdose (92.7%); and dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (92.4%).

Additional analyses of the key risk messages did not demonstrate any notable differences between subgroups of pharmacists.

Among responses to all questions about the safe use of TIRF medicines, there were 2 components of Question 5 relating to the definition of a non-opioid tolerant patient that had low response rates. Despite the high proportion of pharmacists responding correctly to the questions around Key Risk Message 1 (i.e., that patients must be opioid tolerant), only 12.6% of pharmacists correctly indicated that patients considered opioid tolerant are those who are taking regular opioid therapy for 1 week or longer. In addition, 15.6% of pharmacists also correctly indicated that patients not currently taking opioid therapy but who have no known intolerance or hypersensitivity to fentanyl are not considered opioid tolerant. Because the results to Question 5 are discrepant from the other pharmacist results around opioid tolerance (e.g., Questions 6 and 8), it is possible that these results reflect a misunderstanding of the question rather than a lack of understanding of the important safety information. Additional research will be conducted to explore pharmacists' interpretation and understanding of all 3 components of Question 5. The outcome of the research will be included in the next assessment report, and appropriate action may be taken based on the outcome.

Across the 4 key risk messages, pharmacists demonstrated a high level of understanding 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 regardless of route of administration.

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)** **Archimedes Pharma US Inc.** **Cephalon, Inc.** **Endo Pharmaceuticals Inc.** **Insys Therapeutics** **Meda Pharmaceuticals** **Mallinckrodt (a Covidien Company)** **Par Pharmaceutical, Inc.** **ProStrakan, Inc.** **Sandoz, Inc.**
VERSION:	**3.0**
DATE:	**10 SEP 2012**
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LIST OF APPENDICES

1. LIST OF ABBREVIATIONS

CATI	Computer-Assisted Telephone Interviewing
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
ISI	Important Safety Information
KAB	Knowledge, Attitudes and Behavior
REALM	Rapid Estimate of Adult Literacy in Medicine
REMS	Risk Evaluation and Mitigation Strategy
SERP	Safety Event Reporting Plan
TIRF	Transmucosal Immediate Release Fentanyl
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation

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 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 REMS Industry Group (TRIG) includes Archimedes Pharma US Inc., Cephalon, Inc., Endo Pharmaceuticals Inc., Insys Therapeutics, Meda Pharmaceuticals, Mallinckrodt (a Covidien Company), Par Pharmaceutical, Inc., ProStrakan, Inc., and Sandoz Inc.

The Food and Drug Administration (FDA) has determined that a 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 Food and Drug Administration (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 the following 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 the first 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 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 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**
6	Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.	
6a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**TRUE**
6b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	**TRUE**
6c	TIRF medicines may be used in opioid non-tolerant patients.	**FALSE**
6d	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**
8	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.	
8a	Acute or postoperative pain	**NO**
8b	Headache or migraine pain	**NO**
8c	Dental pain	**NO**
8d	Breakthrough pain from cancer	**YES**

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**
6	Please answer “True,” “False,” or “I don’t know” for each statement about TIRF medicines.	
6e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**TRUE**
7	Which of the following are risk factors for opioid abuse? Please answer "Yes," “No,” or “I don’t know” for each option.	
7a	A personal history of psychiatric illness	**YES**
7b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse.	**YES**
9	Please answer “True," “False,” or “I don’t know” for each statement about TIRF medicines.	
9a	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**
9	Please answer “True,” “False,” or “I don’t know” for each statement about TIRF medicines.	
9b	TIRF medicines are interchangeable with each other regardless of route of administration.	**FALSE**
9c	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**
9d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**TRUE**

4.1.2 Additional Questions

Questions about the requirements of the TIRF REMS Access Program, receipt and understanding of the TIRF educational materials, and behaviors will be asked after the key

risk message questions. The following question about behaviors will be asked after the key risk message questions.

Question: How frequently do you perform the following activities when dispensing TIRF medicines?
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

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-respondents from the original sample with subsequent fax, e-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 or outpatient) 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 an 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 the first 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.

Precision of Estimated Rates of Understanding with a Sample Size of 300

(2-sided 95% Confidence Interval)

Estimated Rate of Understanding	Estimated Confidence Interval	
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 (this exclusion only applies to all subsequent waves).

- Pharmacists or their immediate family members who have ever worked for Anesta LLC, Archimedes Pharma US Inc., Cephalon, Inc., Endo Pharmaceuticals Inc., Insys Therapeutics, Meda Pharmaceuticals, Mallinckrodt (a Covidien Company), Par Pharmaceutical, Inc., ProStrakan, Inc., Teva Pharmaceuticals, Ltd., Sandoz Inc., United BioSource Corporation, 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 15-20 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 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 phone. 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 interviews.

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 respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents who completed the survey
- Representativeness of pharmacists based on geography

7.1.1 Description of Primary Analyses

Primary analyses are done for all key risk messages. 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.

7.1.2 Description of Secondary Analyses

Secondary analyses are done only for those key risk messages that contain multiple questions/items. 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.

7.1.3 Analysis Population

The analysis population will be based on eligible pharmacists who completed the survey.

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, Product Complaint, or Medical Information Request. 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 phone) 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 Reporting Plan (SERP). Additional detail regarding processes for adverse event reporting will be specified in the SERP.

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 phone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by phone 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 phone 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.

- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines or a free-text response).

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 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
  - Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV

Survey Legend

– 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 ONLINE/PHONE SURVEY CONTENT]

[PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl 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 Archimedes Pharma US Inc., Cephalon, Inc., Endo Pharmaceuticals Inc., Insys Therapeutics, Meda Pharmaceuticals, Mallinckrodt (a Covidien Company), Par Pharmaceutical, Inc., ProStrakan, and Sandoz 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.

[ONLINE ONLY]How We Use Your Information

[PHONE ONLY] 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 phone number will be used only if there are any questions about your survey responses.

[ONLINE ONLY] How We Protect Your Privacy

[PHONE ONLY]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.

[ONLINE ONLY] How to Learn More about This Survey

[ONLINE ONLY] 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.

[PHONE ONLY]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.

[ONLINE ONLY] Taking the Survey

[ONLINE ONLY] Once you have answered a question and moved on, you cannot go back and change your answers.

[ONLINE ONLY] Thank you for your participation in this survey.

[END 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 **[ONLY TERMINATE AFTER WAVE 1]**
   - ○ No
   - ○ I don't know **[ONLY TERMINATE AFTER WAVE 1]**

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]**
   - ○ Archimedes Pharma US Inc.**[TERMINATE]**
   - ○ Cephalon, Inc. **[TERMINATE]**
   - ○ Endo Pharmaceuticals Inc. **[TERMINATE]**
   - ○ Insys Therapeutics**[TERMINATE]**
   - ○ McKesson Specialty Care Solutions**[TERMINATE]**

- Mallinckrodt (a Covidien Company) **[TERMINATE]**
- Meda Pharmaceuticals **[TERMINATE]**
- Par Pharmaceutical, Inc.**[TERMINATE]**
- ProStrakan, Inc. **[TERMINATE]**
- Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- Sandoz Inc. **[TERMINATE]**
- RelayHealth **[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, patients considered opioid-tolerant are those:

[RANDOMIZE LIST]	True	False	I don't know
5a. Who are taking regular 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 are not currently taking opioid therapy, but with no known intolerance or hypersensitivity to the drug fentanyl	○	○	○

6. Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.

[RANDOMIZE LIST]	True	False	I don't know
6a. TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	○	○	○
6b. Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	○	○	○
6c. TIRF medicines may be used in opioid non-tolerant patients.	○	○	○
6d. 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.	○	○	○
6e. It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	○	○	○

7. 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
7a. A personal history of psychiatric illness	○	○	○
7b. A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	○	○	○
7c. A family history of asthma	○	○	○

8. For which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Answer "Yes," "No," or "I don't know" for each option.

[RANDOMIZE LIST]	Yes	No	I don't know
8a. Acute or postoperative pain	○	○	○
8b. Headache or migraine pain	○	○	○
8c. Dental pain	○	○	○
8d. Breakthrough pain from cancer	○	○	○
8e. Chronic non-cancer pain	○	○	○

9. Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.

[RANDOMIZE LIST]	True	False	I don't know
9a. TIRF medicines can be abused in a manner similar to other opioid agonists.	○	○	○
9b. TIRF medicines are interchangeable with each other regardless of route of administration.	○	○	○
9c. 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.	○	○	○
9d. Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	○	○	○

10. 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
10a.	Ask patients (or their caregivers) about the presence of children in the home	○	○	○	○	○
10b.	Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	○	○	○	○	○
10c.	Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	○	○	○	○	○
10d.	Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	○	○	○	○	○
10e.	Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	○	○	○	○	○
10f.	Give patients (or their caregivers) the Medication Guide for their TIRF medicine	○	○	○	○	○

11. Please answer "True," "False," or "I don't know " for each statement about TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
11a.	TIRF medicines may be sold, loaned, or transferred to another pharmacy.	○	○	○
11b.	All pharmacy staff that dispenses TIRF medicines must be educated on the requirements of the TIRF REMS Access program.	○	○	○

11c. TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.	○	○	○

12. **[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

13. **[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

14. **[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

15. **[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.

16. Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine that you dispense?

- ○ Yes
- ○ No **[GO TO Q18]**
- ○ I don't know **[GO TO Q18]**

17. Did you read the Full Prescribing Information for the TIRF medicine that you dispense?

- ○ Yes
- ○ No
- ○ I don't know

18. Did you receive or do you have access to the Medication Guide for the TIRF medicine that you dispense?

- ○ Yes
- ○ No **[GO TO Q20]**
- ○ I don't know **[GO TO Q20]**

19. Did you read the Medication Guide for the TIRF medicine that you dispense?

- ○ Yes
- ○ No
- ○ I don't know

20. 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]**

21. 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.

22. Are you the Pharmacist in Charge for the TIRF REMS Access Program where you work?

- ○ Yes
- ○ No
- ○ I don't know

23. On average, how many times per month have you dispensed 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

24. Please select the TIRF medicines that you have dispensed within the last 6 months (select all that apply):

- ○ Abstral®
- ○ Actiq® or generic Actiq®
- ○ Fentora® or generic Fentora®
- ○ Lazanda ®
- ○ Onsolis®
- ○ Subsys™

[DEMOGRAPHICS PREAMBLE 2]

These last few questions are for demographic purposes.

25. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

26. 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

27. 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: _____

LAST NAME: _____

ADDRESS: **[MULTILINE INPUT]**

CITY: _____

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: _____

[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: _____

[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 or NAME OF PHARMACIST IN CHARGE]

[STREET_ADDR]

[CITY], [STATE] [ZIP]

Dear [NAME OF PHARMACIST IN CHARGE]:

You were selected to receive this letter because you have enrolled 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 Archimedes Pharma US Inc., Cephalon, Inc., Endo Pharmaceuticals Inc., Insys Therapeutics, Meda Pharmaceuticals, Mallinckrodt (a Covidien Company), Par Pharmaceutical, Inc., ProStrakan, Inc., and Sandoz Inc (collectively referred to as the "TIRF Industry REMS Group"). These manufacturers are looking for 200 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 will only be used to send you a $50 honorarium for the time you took 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 10PM 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,

TIRF Industry REMS Group

* 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.

Appendix B Pharmacy Survey Listings and Subanalysis Tables

Pharmacy Listings

Listing 1 CATEGORIZATION OF VERBATIM RESPONSES TO QUESTION 21 (Questions about the information in the Full Prescribing Information or Medication Guide)

Verbatim Response	Categorized Response
How can I trust a prescription is not being abused without a diagnosis code from MD	Abuse monitoring
How do I take it?? Will it make me tired?	Dosage, side effects
Why should the pharmacist be liable to dispense a medication guide with each fill. Liability and responsibility should be from the prescriber	Medication Guide distribution
Is there an all inclusive guide to dispensing TIRF REMS meds it seems I have to go to each one separately and it's really inconvenient	Medication Guide distribution/format
Meant to answer "no"	General responses
Meant to answer no on previous question	General responses
N/A	General responses
None	General responses
Nothing right now in mind....	General responses
Thanks for sharing these info!	General responses
I need the prescribing information	Prescribing information request
How exactly does filling a prescription for a patient who pays for it cash get properly monitored?? (we do process it to REMSCASH)	REMS process
Who is this monitored by?	REMS process

Listing 2 CATEGORIZATION OF VERBATIM RESPONSES TO REPORTED SAFETY EVENTS OR PRODUCT COMPLAINTS

Verbatim Response	Categorized Response
How can I trust a prescription is not being abused without a diagnosis code from MD	Abuse monitoring
How do I take it?? Will it make me tired?	Dosage, Side effects
How exactly does filling a prescription for a patient who pays for it cash get properly monitored?? (we do process it to REMSCASH)	REMS process
I need the prescribing information	Prescribing Information request
Is there an all inclusive guide to dispensing TIRF REMS meds it seems I have to go to each one separately and it's really inconvenient	Medication Guide distribution/format

Pharmacy Subanalysis Tables

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.

SUBGROUP 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=141		S-2b - 10 to <20 min N=121		S-2c - >= 20 min N=24	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.						
6a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.						
Correct response						
True	122	86.5 (79.8, 91.7)	102	84.3 (76.6, 90.3)	21	87.5 (67.6, 97.3)
Incorrect response						
False	11	7.8	13	10.7	0	0.0
I don't know	8	5.7	6	5.0	3	12.5
6b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.						
Correct response						
True	131	92.9 (87.3, 96.5)	109	90.1 (83.3, 94.8)	22	91.7 (73.0, 99.0)
Incorrect response						
False	3	2.1	2	1.7	0	0.0
I don't know	7	5.0	10	8.3	2	8.3

Question	S-2a - <10 min N=141		S-2b - 10 to <20 min N=121		S-2c - >= 20 min N=24	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
6c: TIRF medicines may be used in opioid non-tolerant patients.						
Correct response						
False	115	81.6 (74.2, 87.6)	89	73.6 (64.8, 81.2)	20	83.3 (62.6, 95.3)
Incorrect response						
True	19	13.5	25	20.7	2	8.3
I don't know	7	5.0	7	5.8	2	8.3
6d: 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	112	79.4 (71.8, 85.8)	91	75.2 (66.5, 82.6)	21	87.5 (67.6, 97.3)
Incorrect response						
False	21	14.9	22	18.2	2	8.3
I don't know	8	5.7	8	6.6	1	4.2

TABLE 6.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUBGROUP 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=141		S-2b - 10 to <20 min N=121		S-2c - >= 20 min N=24	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	2	1.7	0	0.0
1 correct response	8	5.7	3	2.5	2	8.3
2 correct responses	12	8.5	21	17.4	1	4.2
3 correct responses	36	25.5	34	28.1	4	16.7
4 correct responses	85	60.3	61	50.4	17	70.8
Average number of correct responses	3.4	(3.1, 4.0)	3.2	(3.0, 4.0)	3.5	(2.9, 4.0)

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.

SUBGROUP 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=141		S-2b - 10 to <20 min N=121		S-2c - >= 20 min N=24	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 8: 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.						
8a: Acute or postoperative pain						
Correct response						
No	107	75.9 (68.0, 82.7)	97	80.2 (71.9, 86.9)	22	91.7 (73.0, 99.0)
Incorrect response						
Yes	28	19.9	18	14.9	1	4.2
I don't know	6	4.3	6	5.0	1	4.2
8b: Headache or migraine pain						
Correct response						
No	123	87.2 (80.6, 92.3)	111	91.7 (85.3, 96.0)	22	91.7 (73.0, 99.0)
Incorrect response						
Yes	8	5.7	2	1.7	1	4.2
I don't know	10	7.1	8	6.6	1	4.2

Question	S-2a - <10 min N=141		S-2b - 10 to <20 min N=121		S-2c - >= 20 min N=24	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
8c: Dental pain						
Correct response						
No	132	93.6 (88.2, 97.0)	115	95.0 (89.5, 98.2)	23	95.8 (78.9, 99.9)
Incorrect response						
Yes	4	2.8	1	0.8	1	4.2
I don't know	5	3.5	5	4.1	0	0.0
8d: Breakthrough pain from cancer						
Correct response						
Yes	122	86.5 (79.8, 91.7)	96	79.3 (71.0, 86.2)	21	87.5 (67.6, 97.3)
Incorrect response						
No	18	12.8	23	19.0	2	8.3
I don't know	1	0.7	2	1.7	1	4.2

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.

SUBGROUP 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=141		S-2b - 10 to <20 min N=121		S-2c - >= 20 min N=24	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	1	0.7	1	0.8	0	0.0
1 correct response	6	4.3	4	3.3	1	4.2
2 correct responses	5	3.5	9	7.4	1	4.2
3 correct responses	48	34.0	31	25.6	3	12.5
4 correct responses	81	57.4	76	62.8	19	79.2
Average number of correct responses	3.4	(3.2, 4.0)	3.5	(3.2, 4.0)	3.7	(3.0, 4.0)

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.

SUBGROUP 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=141		S-2b - 10 to <20 min N=121		S-2c - >= 20 min N=24	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.						
6e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.						
Correct response						
True	138	97.9 (93.9, 99.6)	118	97.5 (92.9, 99.5)	24	100.0 (85.8, 100.0)
Incorrect response						
False	2	1.4	2	1.7	0	0.0
I don't know	1	0.7	1	0.8	0	0.0
Question 7: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.						
7a: A personal history of psychiatric illness						
Correct response						
Yes	99	70.2 (61.9, 77.6)	76	62.8 (53.6, 71.4)	17	70.8 (48.9, 87.4)
Incorrect response						
No	26	18.4	27	22.3	4	16.7
I don't know	16	11.3	18	14.9	3	12.5

Client: TRIG Project: TIRF KAB

Report Run Date and Time: 11/13/2012 2:13 PM

Question	S-2a - <10 min N=141		S-2b - 10 to <20 min N=121		S-2c - >= 20 min N=24	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
7b: 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	141	100.0 (97.4, 100.0)	120	99.2 (95.5, 100.0)	24	100.0 (85.8, 100.0)
Incorrect response						
No	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	1	0.8	0	0.0
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.						
9a: TIRF medicines can be abused in a manner similar to other opioid agonists.						
Correct response						
True	127	90.1 (83.9, 94.5)	109	90.1 (83.3, 94.8)	22	91.7 (73.0, 99.0)
Incorrect response						
False	9	6.4	8	6.6	2	8.3
I don't know	5	3.5	4	3.3	0	0.0

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.

SUBGROUP 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=141		S-2b - 10 to <20 min N=121		S-2c - >= 20 min N=24	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	1	0.8	0	0.0
1 correct response	0	0.0	0	0.0	0	0.0
2 correct responses	5	3.5	6	5.0	1	4.2
3 correct responses	49	34.8	45	37.2	7	29.2
4 correct responses	87	61.7	69	57.0	16	66.7
Average number of correct responses	3.6	(3.3, 4.0)	3.5	(3.2, 4.0)	3.6	(3.0, 4.0)

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.

SUBGROUP 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=141		S-2b - 10 to <20 min N=121		S-2c - >= 20 min N=24	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.						
9b: TIRF medicines are interchangeable with each other regardless of route of administration.						
Correct response						
False	135	95.7 (91.0, 98.4)	115	95.0 (89.5, 98.2)	23	95.8 (78.9, 99.9)
Incorrect response						
True	2	1.4	5	4.1	1	4.2
I don't know	4	2.8	1	0.8	0	0.0
9c: 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	131	92.9 (87.3, 96.5)	113	93.4 (87.4, 97.1)	21	87.5 (67.6, 97.3)
Incorrect response						
False	4	2.8	5	4.1	1	4.2
I don't know	6	4.3	3	2.5	2	8.3

Question	S-2a - <10 min N=141		S-2b - 10 to <20 min N=121		S-2c - >= 20 min N=24	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.						
Correct response						
True	131	92.9 (87.3, 96.5)	113	93.4 (87.4, 97.1)	23	95.8 (78.9, 99.9)
Incorrect response						
False	6	4.3	2	1.7	0	0.0
I don't know	4	2.8	6	5.0	1	4.2

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.

SUBGROUP 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=141		S-2b - 10 to <20 min N=121		S-2c - >= 20 min N=24	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	1	0.7	1	0.8	1	4.2
1 correct response	3	2.1	1	0.8	0	0.0
2 correct responses	17	12.1	17	14.0	2	8.3
3 correct responses	120	85.1	102	84.3	21	87.5
Average number of correct responses	2.8	(2.6, 3.0)	2.8	(2.6, 3.0)	2.8	(2.2, 3.0)

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=286		S-4b - Telephone N=16	
	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.				
6a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.				
Correct response				
True	245	85.7 (81.1, 89.5)	15	93.8 (69.8, 99.8)
Incorrect response				
False	24	8.4	0	0.0
I don't know	17	5.9	1	6.3
6b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.				
Correct response				
True	262	91.6 (87.8, 94.5)	16	100.0 (79.4, 100.0)
Incorrect response				
False	5	1.7	0	0.0
I don't know	19	6.6	0	0.0

Question	S-4a - Internet N=286		S-4b - Telephone N=16	
	N	% (95% CI)	N	% (95% CI)
6c: TIRF medicines may be used in opioid non-tolerant patients.				
Correct response				
False	224	78.3 (73.1, 83.0)	13	81.3 (54.4, 96.0)
Incorrect response				
True	46	16.1	2	12.5
I don't know	16	5.6	1	6.3
6d: 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	224	78.3 (73.1, 83.0)	13	81.3 (54.4, 96.0)
Incorrect response				
False	45	15.7	1	6.3
I don't know	17	5.9	2	12.5

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=286		S-4b - Telephone N=16	
	N	% (95% CI)	N	% (95% CI)
Question 8: 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.				
8a: Acute or postoperative pain				
Correct response				
No	226	79.0 (73.8, 83.6)	10	62.5 (35.4, 84.8)
Incorrect response				
Yes	47	16.4	5	31.3
I don't know	13	4.5	1	6.3
8b: Headache or migraine pain				
Correct response				
No	256	89.5 (85.4, 92.8)	13	81.3 (54.4, 96.0)
Incorrect response				
Yes	11	3.8	1	6.3
I don't know	19	6.6	2	12.5

Question	S-4a - Internet N=286		S-4b - Telephone N=16	
	N	% (95% CI)	N	% (95% CI)
8c: Dental pain				
Correct response				
No	270	94.4 (91.1, 96.8)	16	100.0 (79.4, 100.0)
Incorrect response				
Yes	6	2.1	0	0.0
I don't know	10	3.5	0	0.0
8d: Breakthrough pain from cancer				
Correct response				
Yes	239	83.6 (78.8, 87.7)	13	81.3 (54.4, 96.0)
Incorrect response				
No	43	15.0	3	18.8
I don't know	4	1.4	0	0.0

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=286		S-4b - Telephone N=16	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	2	0.7	0	0.0
1 correct response	11	3.8	0	0.0
2 correct responses	15	5.2	4	25.0
3 correct responses	82	28.7	4	25.0
4 correct responses	176	61.5	8	50.0
Average number of correct responses	3.5	(3.3, 4.0)	3.3	(2.5, 4.0)

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=286		S-4b - Telephone N=16	
	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.				
6e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.				
Correct response				
True	280	97.9 (95.5, 99.2)	15	93.8 (69.8, 99.8)
Incorrect response				
False	4	1.4	1	6.3
I don't know	2	0.7	0	0.0
Question 7: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.				
7a: A personal history of psychiatric illness				
Correct response				
Yes	192	67.1 (61.4, 72.5)	9	56.3 (29.9, 80.2)
Incorrect response				
No	57	19.9	5	31.3
I don't know	37	12.9	2	12.5

Question	S-4a - Internet N=286		S-4b - Telephone N=16	
	N	% (95% CI)	N	% (95% CI)
7b: 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	285	99.7 (98.1, 100.0)	16	100.0 (79.4, 100.0)
Incorrect response				
No	0	0.0	0	0.0
I don't know	1	0.3	0	0.0
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.				
9a: TIRF medicines can be abused in a manner similar to other opioid agonists.				
Correct response				
True	258	90.2 (86.2, 93.4)	15	93.8 (69.8, 99.8)
Incorrect response				
False	19	6.6	0	0.0
I don't know	9	3.1	1	6.3

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=286		S-4b - Telephone N=16	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	1	0.3	0	0.0
1 correct response	0	0.0	0	0.0
2 correct responses	12	4.2	1	6.3
3 correct responses	101	35.3	7	43.8
4 correct responses	172	60.1	8	50.0
Average number of correct responses	3.5	(3.4, 4.0)	3.4	(2.7, 4.0)

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=286		S-4b - Telephone N=16	
	N	% (95% CI)	N	% (95% CI)
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.				
9b: TIRF medicines are interchangeable with each other regardless of route of administration.				
Correct response				
False	273	95.5 (92.4, 97.6)	14	87.5 (61.7, 98.4)
Incorrect response				
True	8	2.8	1	6.3
I don't know	5	1.7	1	6.3
9c: 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	265	92.7 (89.0, 95.4)	15	93.8 (69.8, 99.8)
Incorrect response				
False	10	3.5	0	0.0
I don't know	11	3.8	1	6.3

Question	S-4a - Internet N=286		S-4b - Telephone N=16	
	N	% (95% CI)	N	% (95% CI)
9d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.				
Correct response				
True	267	93.4 (89.8, 96.0)	12	75.0 (47.6, 92.7)
Incorrect response				
False	8	2.8	2	12.5
I don't know	11	3.8	2	12.5

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=286		S-4b - Telephone N=16	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	3	1.0	0	0.0
1 correct response	4	1.4	1	6.3
2 correct responses	36	12.6	5	31.3
3 correct responses	243	85.0	10	62.5
Average number of correct responses	2.8	(2.7, 3.0)	2.6	(1.9, 3.0)

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.

SUBGROUP ANALYSIS 5: TIME PRACTICING AS A PHARMACIST (QUESTION 26)

- **S-5a - Less than 3 years**
- **S-5b – 3 to 5 years**
- **S-5c – 5 to 15 years**
- **S-5d – More than 15 years**

Question	S-5a Less than 3 years N=25		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=88		S-5d More than 15 years N=145	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
6a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.								
Correct response								
True	24	96.0 (79.6, 99.9)	38	92.7 (80.1, 98.5)	76	86.4 (77.4, 92.8)	119	82.1 (74.8, 87.9)
Incorrect response								
False	0	0.0	1	2.4	8	9.1	15	10.3
I don't know	1	4.0	2	4.9	4	4.5	11	7.6

Question	S-5a Less than 3 years N=25		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=88		S-5d More than 15 years N=145	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
6b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.								
Correct response								
True	24	96.0 (79.6, 99.9)	40	97.6 (87.1, 99.9)	77	87.5 (78.7, 93.6)	134	92.4 (86.8, 96.2)
Incorrect response								
False	0	0.0	0	0.0	2	2.3	3	2.1
I don't know	1	4.0	1	2.4	9	10.2	8	5.5
6c: TIRF medicines may be used in opioid non-tolerant patients.								
Correct response								
False	22	88.0 (68.8, 97.5)	35	85.4 (70.8, 94.4)	72	81.8 (72.2, 89.2)	105	72.4 (64.4, 79.5)
Incorrect response								
True	2	8.0	3	7.3	11	12.5	32	22.1
I don't know	1	4.0	3	7.3	5	5.7	8	5.5
6d: 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	19	76.0 (54.9, 90.6)	33	80.5 (65.1, 91.2)	72	81.8 (72.2, 89.2)	112	77.2 (69.5, 83.8)
Incorrect response								
False	3	12.0	8	19.5	11	12.5	24	16.6
I don't know	3	12.0	0	0.0	5	5.7	9	6.2

TABLE 6.2.5 SECONDARY 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 26):

- **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=25		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=88		S-5d More than 15 years N=145	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	1	1.1	1	0.7
1 correct response	0	0.0	1	2.4	5	5.7	7	4.8
2 correct responses	2	8.0	2	4.9	8	9.1	22	15.2
3 correct responses	7	28.0	11	26.8	20	22.7	41	28.3
4 correct responses	16	64.0	27	65.9	54	61.4	74	51.0
Average number of correct responses	3.6	(2.9, 4.0)	3.6	(3.1, 4.0)	3.4	(3.1, 4.0)	3.2	(3.0, 4.0)

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 26):

- **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=25		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=88		S-5d More than 15 years N=145	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 8: 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.								
8a: Acute or postoperative pain								
Correct response								
No	22	88.0 (68.8, 97.5)	33	80.5 (65.1, 91.2)	72	81.8 (72.2, 89.2)	107	73.8 (65.8, 80.7)
Incorrect response								
Yes	2	8.0	7	17.1	13	14.8	29	20.0
I don't know	1	4.0	1	2.4	3	3.4	9	6.2

Question	S-5a Less than 3 years N=25		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=88		S-5d More than 15 years N=145	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
8b: Headache or migraine pain								
Correct response								
No	25	100.0 (86.3, 100.0)	39	95.1 (83.5, 99.4)	78	88.6 (80.1, 94.4)	124	85.5 (78.7, 90.8)
Incorrect response								
Yes	0	0.0	1	2.4	4	4.5	7	4.8
I don't know	0	0.0	1	2.4	6	6.8	14	9.7
8c: Dental pain								
Correct response								
No	25	100.0 (86.3, 100.0)	40	97.6 (87.1, 99.9)	82	93.2 (85.7, 97.5)	136	93.8 (88.5, 97.1)
Incorrect response								
Yes	0	0.0	1	2.4	4	4.5	1	0.7
I don't know	0	0.0	0	0.0	2	2.3	8	5.5
8d: Breakthrough pain from cancer								
Correct response								
Yes	23	92.0 (74.0, 99.0)	34	82.9 (67.9, 92.8)	72	81.8 (72.2, 89.2)	121	83.4 (76.4, 89.1)
Incorrect response								
No	2	8.0	7	17.1	14	15.9	22	15.2
I don't know	0	0.0	0	0.0	2	2.3	2	1.4

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 26):

- **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=25		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=88		S-5d More than 15 years N=145	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	1	1.1	1	0.7
1 correct response	0	0.0	1	2.4	3	3.4	7	4.8
2 correct responses	0	0.0	1	2.4	8	9.1	10	6.9
3 correct responses	5	20.0	13	31.7	19	21.6	47	32.4
4 correct responses	20	80.0	26	63.4	57	64.8	80	55.2
Average number of correct responses	3.8	(3.2, 4.0)	3.6	(3.1, 4.0)	3.5	(3.1, 4.0)	3.4	(3.1, 4.0)

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 26):

- **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=25		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=88		S-5d More than 15 years N=145	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
6e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.								
Correct response								
True	25	100.0 (86.3, 100.0)	41	100.0 (91.4, 100.0)	83	94.3 (87.2, 98.1)	143	98.6 (95.1, 99.8)
Incorrect response								
False	0	0.0	0	0.0	4	4.5	1	0.7
I don't know	0	0.0	0	0.0	1	1.1	1	0.7

Question	S-5a Less than 3 years N=25		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=88		S-5d More than 15 years N=145	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.								
7a: A personal history of psychiatric illness								
Correct response								
Yes	16	64.0 (42.5, 82.0)	31	75.6 (59.7, 87.6)	57	64.8 (53.9, 74.7)	94	64.8 (56.5, 72.6)
Incorrect response								
No	6	24.0	6	14.6	22	25.0	28	19.3
I don't know	3	12.0	4	9.8	9	10.2	23	15.9
7b: 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	25	100.0 (86.3, 100.0)	41	100.0 (91.4, 100.0)	87	98.9 (93.8, 100.0)	145	100.0 (97.5, 100.0)
Incorrect response								
No	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	1	1.1	0	0.0
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
9a: TIRF medicines can be abused in a manner similar to other opioid agonists.								
Correct response								
True	22	88.0 (68.8, 97.5)	35	85.4 (70.8, 94.4)	78	88.6 (80.1, 94.4)	135	93.1 (87.7, 96.6)
Incorrect response								
False	3	12.0	5	12.2	5	5.7	6	4.1
I don't know	0	0.0	1	2.4	5	5.7	4	2.8

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 26):

- **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=25		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=88		S-5d More than 15 years N=145	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	1	1.1	0	0.0
1 correct response	0	0.0	0	0.0	0	0.0	0	0.0
2 correct responses	1	4.0	2	4.9	5	5.7	5	3.4
3 correct responses	10	40.0	12	29.3	33	37.5	53	36.6
4 correct responses	14	56.0	27	65.9	49	55.7	87	60.0
Average number of correct responses	3.5	(2.9, 4.0)	3.6	(3.1, 4.0)	3.5	(3.1, 4.0)	3.6	(3.3, 4.0)

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 26):

- **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=25		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=88		S-5d More than 15 years N=145	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
9b: TIRF medicines are interchangeable with each other regardless of route of administration.								
Correct response								
False	25	100.0 (86.3, 100.0)	40	97.6 (87.1, 99.9)	82	93.2 (85.7, 97.5)	137	94.5 (89.4, 97.6)
Incorrect response								
True	0	0.0	1	2.4	4	4.5	4	2.8
I don't know	0	0.0	0	0.0	2	2.3	4	2.8

Question	S-5a Less than 3 years N=25		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=88		S-5d More than 15 years N=145	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9c: 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	24	96.0 (79.6, 99.9)	41	100.0 (91.4, 100.0)	76	86.4 (77.4, 92.8)	137	94.5 (89.4, 97.6)
Incorrect response								
False	0	0.0	0	0.0	7	8.0	3	2.1
I don't know	1	4.0	0	0.0	5	5.7	5	3.4
9d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.								
Correct response								
True	25	100.0 (86.3, 100.0)	37	90.2 (76.9, 97.3)	84	95.5 (88.8, 98.7)	130	89.7 (83.5, 94.1)
Incorrect response								
False	0	0.0	2	4.9	1	1.1	7	4.8
I don't know	0	0.0	2	4.9	3	3.4	8	5.5

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 26):

- **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=25		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=88		S-5d More than 15 years N=145	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	2	2.3	1	0.7
1 correct response	0	0.0	0	0.0	1	1.1	4	2.8
2 correct responses	1	4.0	5	12.2	14	15.9	20	13.8
3 correct responses	24	96.0	36	87.8	71	80.7	120	82.8
Average number of correct responses	3.0	(2.4, 3.0)	2.9	(2.4, 3.0)	2.8	(2.5, 3.0)	2.8	(2.6, 3.0)

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.

SUBGROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSING TIRF MEDICINES WITHIN THE LAST 6 MONTHS

- **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=122		S-6b 1 - 2 N=102		S-6c 3 - 5 N=29		S-6d More than 5 N=23	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
6a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.								
Correct response								
True	110	90.2 (83.4, 94.8)	85	83.3 (74.7, 90.0)	24	82.8 (64.2, 94.2)	20	87.0 (66.4, 97.2)
Incorrect response								
False	5	4.1	15	14.7	0	0.0	3	13.0
I don't know	7	5.7	2	2.0	5	17.2	0	0.0

Question	S-6a None N=122		S-6b 1 - 2 N=102		S-6c 3 - 5 N=29		S-6d More than 5 N=23	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
6b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.								
Correct response								
True	117	95.9 (90.7, 98.7)	93	91.2 (83.9, 95.9)	26	89.7 (72.6, 97.8)	21	91.3 (72.0, 98.9)
Incorrect response								
False	2	1.6	3	2.9	0	0.0	0	0.0
I don't know	3	2.5	6	5.9	3	10.3	2	8.7
6c: TIRF medicines may be used in opioid non-tolerant patients.								
Correct response								
False	101	82.8 (74.9, 89.0)	77	75.5 (66.0, 83.5)	21	72.4 (52.8, 87.3)	19	82.6 (61.2, 95.0)
Incorrect response								
True	15	12.3	17	16.7	7	24.1	4	17.4
I don't know	6	4.9	8	7.8	1	3.4	0	0.0
6d: 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	104	85.2 (77.7, 91.0)	73	71.6 (61.8, 80.1)	23	79.3 (60.3, 92.0)	19	82.6 (61.2, 95.0)
Incorrect response								
False	13	10.7	21	20.6	5	17.2	3	13.0
I don't know	5	4.1	8	7.8	1	3.4	1	4.3

TABLE 6.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUBGROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSING TIRF MEDICINES WITHIN THE LAST 6 MONTHS

- **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=122		S-6b 1 - 2 N=102		S-6c 3 - 5 N=29		S-6d More than 5 N=23	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	0	0.0	1	4.3
1 correct response	3	2.5	6	5.9	3	10.3	0	0.0
2 correct responses	9	7.4	16	15.7	2	6.9	2	8.7
3 correct responses	29	23.8	30	29.4	9	31.0	5	21.7
4 correct responses	81	66.4	50	49.0	15	51.7	15	65.2
Average number of correct responses	3.5	(3.3, 4.0)	3.2	(2.9, 4.0)	3.2	(2.7, 4.0)	3.4	(2.8, 4.0)

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.

SUBGROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSING TIRF MEDICINES WITHIN THE LAST 6 MONTHS

- **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=122		S-6b 1 - 2 N=102		S-6c 3 - 5 N=29		S-6d More than 5 N=23	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 8: 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.								
8a: Acute or postoperative pain								
Correct response								
No	99	81.1 (73.1, 87.7)	85	83.3 (74.7, 90.0)	18	62.1 (42.3, 79.3)	17	73.9 (51.6, 89.8)
Incorrect response								
Yes	19	15.6	14	13.7	10	34.5	4	17.4
I don't know	4	3.3	3	2.9	1	3.4	2	8.7

Question	S-6a None N=122		S-6b 1 - 2 N=102		S-6c 3 - 5 N=29		S-6d More than 5 N=23	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
8b: Headache or migraine pain								
Correct response								
No	111	91.0 (84.4, 95.4)	95	93.1 (86.4, 97.2)	22	75.9 (56.5, 89.7)	22	95.7 (78.1, 99.9)
Incorrect response								
Yes	3	2.5	2	2.0	4	13.8	0	0.0
I don't know	8	6.6	5	4.9	3	10.3	1	4.3
8c: Dental pain								
Correct response								
No	119	97.5 (93.0, 99.5)	98	96.1 (90.3, 98.9)	27	93.1 (77.2, 99.2)	23	100.0 (85.2, 100.0)
Incorrect response								
Yes	1	0.8	1	1.0	1	3.4	0	0.0
I don't know	2	1.6	3	2.9	1	3.4	0	0.0
8d: Breakthrough pain from cancer								
Correct response								
Yes	104	85.2 (77.7, 91.0)	89	87.3 (79.2, 93.0)	23	79.3 (60.3, 92.0)	14	60.9 (38.5, 80.3)
Incorrect response								
No	17	13.9	13	12.7	5	17.2	8	34.8
I don't know	1	0.8	0	0.0	1	3.4	1	4.3

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.

SUBGROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSING TIRF MEDICINES WITHIN THE LAST 6 MONTHS

- **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=122		S-6b 1 - 2 N=102		S-6c 3 - 5 N=29		S-6d More than 5 N=23	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	1	3.4	0	0.0
1 correct response	3	2.5	3	2.9	1	3.4	0	0.0
2 correct responses	6	4.9	3	2.9	3	10.3	3	13.0
3 correct responses	34	27.9	26	25.5	13	44.8	10	43.5
4 correct responses	79	64.8	70	68.6	11	37.9	10	43.5
Average number of correct responses	3.5	(3.3, 4.0)	3.6	(3.3, 4.0)	3.1	(2.6, 4.0)	3.3	(2.7, 4.0)

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.

SUBGROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSING TIRF MEDICINES WITHIN THE LAST 6 MONTHS

- **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=122		S-6b 1 - 2 N=102		S-6c 3 - 5 N=29		S-6d More than 5 N=23	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
6e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.								
Correct response								
True	121	99.2 (95.5, 100.0)	99	97.1 (91.6, 99.4)	29	100.0 (88.1, 100.0)	23	100.0 (85.2, 100.0)
Incorrect response								
False	1	0.8	3	2.9	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0	0	0.0

Question	S-6a None N=122		S-6b 1 - 2 N=102		S-6c 3 - 5 N=29		S-6d More than 5 N=23	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.								
7a: A personal history of psychiatric illness								
Correct response								
Yes	78	63.9 (54.7, 72.4)	73	71.6 (61.8, 80.1)	17	58.6 (38.9, 76.5)	16	69.6 (47.1, 86.8)
Incorrect response								
No	30	24.6	16	15.7	6	20.7	5	21.7
I don't know	14	11.5	13	12.7	6	20.7	2	8.7
7b: 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	122	100.0 (97.0, 100.0)	102	100.0 (96.4, 100.0)	29	100.0 (88.1, 100.0)	23	100.0 (85.2, 100.0)
Incorrect response								
No	0	0.0	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 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
9a: TIRF medicines can be abused in a manner similar to other opioid agonists.								
Correct response								
True	110	90.2 (83.4, 94.8)	94	92.2 (85.1, 96.6)	26	89.7 (72.6, 97.8)	22	95.7 (78.1, 99.9)
Incorrect response								
False	6	4.9	6	5.9	2	6.9	1	4.3
I don't know	6	4.9	2	2.0	1	3.4	0	0.0

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.

SUBGROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSING TIRF MEDICINES WITHIN THE LAST 6 MONTHS

- **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=122		S-6b 1 - 2 N=102		S-6c 3 - 5 N=29		S-6d More than 5 N=23	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
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	7	5.7	4	3.9	0	0.0	0	0.0
3 correct responses	43	35.2	32	31.4	15	51.7	8	34.8
4 correct responses	72	59.0	66	64.7	14	48.3	15	65.2
Average number of correct responses	3.5	(3.3, 4.0)	3.6	(3.3, 4.0)	3.5	(2.9, 4.0)	3.7	(3.0, 4.0)

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.

SUBGROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 23)

- **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=122		S-6b 1 - 2 N=102		S-6c 3 - 5 N=29		S-6d More than 5 N=23	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
9b: TIRF medicines are interchangeable with each other regardless of route of administration.								
Correct response								
False	119	97.5 (93.0, 99.5)	94	92.2 (85.1, 96.6)	29	100.0 (88.1, 100.0)	23	100.0 (85.2, 100.0)
Incorrect response								
True	2	1.6	4	3.9	0	0.0	0	0.0
I don't know	1	0.8	4	3.9	0	0.0	0	0.0

Question	S-6a None N=122		S-6b 1 - 2 N=102		S-6c 3 - 5 N=29		S-6d More than 5 N=23	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9c: 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	111	91.0 (84.4, 95.4)	96	94.1 (87.6, 97.8)	29	100.0 (88.1, 100.0)	22	95.7 (78.1, 99.9)
Incorrect response								
False	5	4.1	4	3.9	0	0.0	1	4.3
I don't know	6	4.9	2	2.0	0	0.0	0	0.0
9d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.								
Correct response								
True	117	95.9 (90.7, 98.7)	92	90.2 (82.7, 95.2)	25	86.2 (68.3, 96.1)	21	91.3 (72.0, 98.9)
Incorrect response								
False	1	0.8	5	4.9	3	10.3	1	4.3
I don't know	4	3.3	5	4.9	1	3.4	1	4.3

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.

SUBGROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 23)

- **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=122		S-6b 1 - 2 N=102		S-6c 3 - 5 N=29		S-6d More than 5 N=23	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	2	1.6	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	5	4.9	0	0.0	0	0.0
2 correct responses	13	10.7	14	13.7	4	13.8	3	13.0
3 correct responses	107	87.7	83	81.4	25	86.2	20	87.0
Average number of correct responses	2.8	(2.6, 3.0)	2.8	(2.5, 3.0)	2.9	(2.3, 3.0)	2.9	(2.3, 3.0)

11.4.3 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	Final Wave 1, Version 1.0
Product Name:	Transmucosal Immediate Release Fentanyl
Sponsor:	**TIRF REMS Industry Group (TRIG) of Companies:** Archimedes Pharma US, Inc. Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Insys Therapeutics Meda Pharmaceuticals Mallinckrodt (the Pharmaceuticals Business of Covidien) Par Pharmaceutical, Inc. ProStrakan, Inc.
Date:	14 December 2012

Confidentiality Statement

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LIST OF ABBREVIATIONS

ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
KAB	Knowledge, Attitudes, and Behavior
PI	Prescribing Information
REMS	Risk Evaluation and Mitigation Strategy
SAP	Statistical Analysis Plan
SERP	Safety Event Reporting Plan
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

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 Archimedes Pharma United States (US) Inc., Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.), Insys Therapeutics, Meda Pharmaceuticals, Mallinckrodt (the Pharmaceuticals Business of Covidien), Par Pharmaceutical, Inc., and ProStrakan, Inc. At the time of protocol development for the Knowledge, Attitude, and Behavior (KAB) surveys, Sandoz was also a member of the TRIG; however Sandoz terminated their involvement in the TIRF REMS Access program, effective 15 September 2012.

The Food and Drug Administration (FDA) has determined that a class-wide 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 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. The protocol describes 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.

Results from the surveys will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

2. PRESCRIBER SURVEY OBJECTIVES

The evaluation survey uses a questionnaire to document the level of knowledge and assess the attitudes and behavior of prescribers 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 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 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 prescribers who were enrolled in the TIRF REMS Access program as of 15 August 2012. A target sample of 300 prescribers who were enrolled in the TIRF REMS Access program were surveyed from 24 September 2012 to 30 October 2012. The size of the sample was determined based on both practical and statistical considerations.

Subject recruitment was from a random sample of prescribers who were enrolled in the TIRF REMS Access program. Respondents or respondents' 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 first wave of the TIRF survey will not be eligible to participate in subsequent survey waves.

Potential subjects were recruited via a letter sent through the United States Postal Service, and email (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, a second mailing was sent to non-respondents from the original sample with subsequent email, or mail to maximize participation. If these efforts did not result in the required number of surveys within 21 days, then an additional sample of potential subjects was randomly selected.

Prescribers were given the option of taking the survey by telephone via the Survey Coordinating Center 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 the specific contraindications for TIRF medicines opioid non-tolerant patients.

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired response**
6	Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.	
6a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	***True***
6b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	***True***
6c	TIRF medicines may be used to treat opioid non-tolerant patients.	***False***
6d	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.

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**
8	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.	
8a	Acute or postoperative pain	***No***
8b	Headache or migraine pain	***No***
8c	Dental pain	***No***
8d	Breakthrough pain from cancer	***Yes***

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**
6	Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.	
6e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	***True***
7	Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.	
7a	A personal history of psychiatric illness	***Yes***
7b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	***Yes***
9	Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.	
9a	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**
9	Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.	
9b	TIRF medicines are interchangeable with each other regardless of route of administration.	**False**
9c	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**
9d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**True**

3.3 Additional Questions

The survey also contained 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 was asked after the key risk message questions:

Question : How frequently do you perform the following activities when prescribing TIRF medicines?
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.

4. STATISTICAL METHODS

4.1 Study Population

4.1.1 Primary Analysis Population

According to the prospective Statistical Analysis Plan (SAP), 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 Question 3 (enrolled in the TIRF REMS Access program), and ***No*** to Question 2 (participated in past survey; not applicable for Wave 1) and 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 as appropriate were answered. Note that some questions may not be answered because of skip logic in the survey questionnaire.

4.1.2 Subpopulations of Interest

The following subgroup analyses were conducted if the subgroup included at least 20 respondents.

- Subpopulation S-1:

a) Prescribers who received and read the TIRF medicine educational materials (***Yes*** for Question 18 [Full Prescribing Information], or ***Yes*** for Question 20 [Medication Guide]).

b) Prescribers who did not read the full prescribing information for the TIRF medicine educational materials (***No or I don't know*** for Question 18 [Full Prescribing Information], or ***No or I don't know*** for Question 20 [Medication Guide]).

- Subpopulation S-2: Medical degree (***MD, DO, Nurse Practitioner or Physician Assistant*** for Question 29);
- Subpopulation S-3: Time to complete survey-Internet (***<10 min, 10 to <20 min, or ≥20 min***);
- Subpopulation S-4: Time to complete survey-Telephone (***<10 min, 10 to <20 min, or ≥20 min***);
- Subpopulation S-5: Modality to complete survey (***Internet or Telephone***)
- Subpopulation S-6: Time practicing medicine (***less than 3 years, 3 to 5 years, 6 to 15 years, or more than 15 years*** for Question 30);
- Subpopulation S-7: Number of times per month prescribing TIRF medicines with the last 6 months (***None, 1-2 times, 3-5 times, or more than 5 times a month*** for Question 26).

4.1.2.2 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/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).

4.1.2.3 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.

4.1.3 Prescriber Report of Adverse Event, Product Complaint, or Medical Information Request During Survey

A prescriber may have reported an adverse event or other safety event experienced by their patients while taking a TIRF product either in free text fields on the survey or while in conversation with the Survey Coordinating Center. If the event was mentioned to a Survey Coordinating Center 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 manufacturer might contact them to obtain additional information about the safety event. The Internet surveys were monitored for any comments recorded in the free text fields. Information on all reports (Internet or Telephone) that constituted an adverse event or other safety event was forwarded to the appropriate TIRF

medicine manufacturer for processing within 1 business day of awareness of the event as outlined in the Safety Event Reporting Plan (SERP).

5. RESULTS

Results of the prescriber responses to questions in the KAB survey are summarized in this section.

5.1 Survey Participants

5.1.1 Survey Participant Administration Results

A total of 5330 prescribers were sent letters inviting them to participate in this survey (Table 1). An additional 3505 reminder letters were sent. Prescribers may have received more than 1 reminder letter.

In all, a total of 302 prescribers expressed interest in the survey, met the eligibility criteria, and completed the survey. Of these 302 prescribers, 293 (81.8%) completed the survey online, and 9 (2.5%) completed it by telephone (Table 3).

From the 302 respondents, 303 surveys were collected. It was identified that 1 respondent completed the survey twice. Only the first completed survey was included in the analysis for this respondent.

Based on the TRIG Sponsors interpretation of state laws regarding prescriber reimbursement, respondents from Massachusetts (MA), Vermont (VT), and Minnesota (MN) were not eligible to receive the $125 honorarium. Letters were sent to prescribers in these states, and 2 respondents from these states (MA and MN) chose to participate, but were not paid.

Table 1. Survey Participant Administration Results

Summary Statistic	Screened Prescribers N=358[1]	
	All Respondents	
	N	%
Number of invitations issued to prescribers	5330	
Number of reminder letters issued to prescribers	3505	
Number of prescribers screened for participation	358[1]	
Number of prescribers eligible for participation	302	
Number of prescribers completing the survey	302	84.4
By telephone	9	2.5
By internet	293	81.8

[1] This is the denominator for the percentages in this table (N=358).

As shown in Table 2, a total of 358 prescribers agreed to participate in this survey and of those 315 prescribers were enrolled in the TIRF REMs Access program; 43 prescribers were ineligible because they were not enrolled in the program or they did not know whether they were enrolled. Eleven respondents were ineligible for the survey because they, or an immediate family member, had worked for UBC or a TRIG company in the past, or did not know whether they, or an immediate family member, had worked for a TRIG company, UBC, RelayHealth, McKesson Specialty Care Solutions, or FDA in the past, and 2 prescribers preferred not to answer and thus were considered ineligible.

Of note, following the close of the survey, the Survey Coordinating Center received information that a nurse had completed the survey as if she were a TIRF medicines prescriber in the office in which she works, (i.e., answered Male as gender and DO as medical degree). Since the survey was already closed, this respondent remained in the data as 1 of the 302 eligible and completed prescribers.

Table 2. Survey Participant Screening Results

Question	All Respondents N=358		Eligible Completed Prescribers N=302	
	n	%	n	%
Question 1: Do you agree to participate in this survey?				
Yes	358	100.0	302	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	8	2.2	5	1.7
No	331	92.5	283	93.7
I don't know	19	5.3	14	4.6
Question not asked[2]	0	0.0		
Question 3: Are you enrolled in the TIRF REMS Access program?				
Yes	315	88.0	302	100.0
No[1]	15	4.2		
I don't know[1]	28	7.8		
Question not asked [2]	0	0.0		

(continued)

Table 2. Survey Participant Screening Results

Question	All Respondents N=358		Eligible Completed Prescribers N=302	
	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		
Archimedes Pharma US, Inc.[1]	1	0.3		
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)[1]	2	0.6		
Endo Pharmaceuticals, Inc.[1]	1	0.3		
Insys Therapeutics[1]	3	0.8		
McKesson Specialty Care Solutions[1]	0	0.0		
Mallinckrodt (the Pharmaceuticals Business of Covidien)[1]	0	0.0		
Meda Pharmaceuticals[1]	0	0.0		
Par Pharmaceutical, Inc.[1]	0	0.0		
ProStrakan, Inc.[1]	0	0.0		
Sandoz, Inc.[1]	0	0.0		
Teva Pharmaceuticals, Ltd.[1]	1	0.3		
RelayHealth[1]	0	0.0		
United BioSource Corporation[1]	1	0.3		
FDA[1]	0	0.0		
None of these apply[4]	302	84.4	302	100.0
I don't know[1]	7	2.0		
Prefer not to answer[1]	2	0.6		
Question not asked[2]	43	12.0		

[1] Ineligible to participate in the survey.

[2] Question not asked due to a previous question elimination.

[3] More than 1 response can be selected, so percentages may not sum to 100%.

[4] Ineligible if selected in addition to another response.

Those taking the survey online took a mean of 17.2 minutes to complete, while those taking it by telephone took a mean of 24.2 minutes.

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

Summary Statistic	Telephone	Internet	Total [1]
N	9	293	302
Mean (Standard Deviation)	24.2 (5.80)	17.2 (8.49)	17.5 (8.50)
Minimum	13	6	6
Median	24.7	14.8	14.9
Maximum	34	64	64
Category			
0 – <5 Minutes	0	0	0
5 – <10 Minutes	0	35	35
10 – <15 Minutes	1	116	117
15 – <20 Minutes	0	65	65
20 – <25 Minutes	5	28	33
25 – <30 Minutes	2	28	30
30 Minutes or More	1	21	22

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

5.1.2 Prescriber Demographic and TIRF Product Prescribing Characteristics

The demographic characteristics of enrolled prescribers are shown in Table 4.

The majority of respondents were male (59.6%). Respondents from the South, West, and Northeast included 31.1%, 26.8%, and 25.2% of the survey population, respectively; while respondents from the Midwest region of the US composed 16.9%, of the total survey population. The proportion of eligible completed prescribers within each geographic region was similar to the overall proportion of prescribers (7701 prescribers enrolled in the TIRF REMS Access program as of 15 August 2012) in each geographic region (Table 4). The most common healthcare degree was an MD (57.0%), and the most common medical specialties were pain management (50.7%) and oncology (22.5%). Of respondents who were medical doctors, half of the respondents (50.7%) had practiced medicine for more than 15 years.

Table 4. Demographic Characteristics of Eligible Prescribers

Question	Eligible Completed Prescribers N=302[1]	
	n	%
Question 28: What is your gender?		
Male	180	59.6
Female	116	38.4
Prefer not to answer	6	2.0
Question 29: What is your medical degree?		
MD	172	57.0
DO	26	8.6
Nurse Practitioner	55	18.2
Physician's Assistant	46	15.2
Prefer not to answer	3	1.0
Question 30: In total, how many years have you been practicing medicine, since completing your post-graduate education?[2]		
Less than 3 years	12	6.0
3-5 years	14	7.0
6-10 years	36	17.9
11-15 years	36	17.9
More than 15 years	102	50.7
Prefer not to answer	1	0.5
Question 32: What is your medical specialty?		
Oncology	68	22.5
Primary Care	46	15.2
Pain Management	153	50.7
Other (please specify)[3]	35	11.6

(continued)

Table 4. Demographic Characteristics of Eligible Prescribers

Question	Eligible Completed Prescribers N=302[1]			
	n		%	
Question 31: In which state or US Territory do you practice?[4]				
Geographic Region	**Eligible Completed Respondents N=302**		**Enrolled in TIRF REMS Access Program on 15AUG2012 N=7701**	
	n	**%**	**n**	**%**
Northeast	76	25.2	1643	21.3
Midwest	51	16.9	1352	17.6
South	94	31.1	2811	36.5
West	81	26.8	1893	24.6
Other	0	0.0	2	0.03
Prefer not to answer	0	0.0		

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

[2] This question is presented only to a sub-group of prescribers. Percentages are based on the number of prescribers to whom this question was presented.

[3] Other medical specialties are presented in Appendix B, Listing 3.

[4] According to the 2001 Geographic Area Regions set by the US Census Bureau, 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. Other includes Puerto Rico. Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

Of prescribers who described their medical specialty as 'other' (see Table 4), 5.0% stated their medical specialty was General Medicine, followed by Neurology and Rehabilitation (1.7% each), (Table 5).

Table 5. Categorized Responses for Respondents Who Answered "Other" to Question 32

Response (Categorized Type) [2]	Eligible Completed Prescribers N=302[1]	
	n [3]	%
General Medicine	15	5.0%
Neurology	5	1.7%
Rehabilitation	5	1.7%
Emergency Medicine	2	0.7%
Psychiatry	2	0.7%
Anesthesiology	1	0.3%
Gerontology	1	0.3%
Oncology - Gynecology	1	0.3%
Oncology - Hematology	1	0.3%
Oncology - Radiology	1	0.3%
Rheumatology	1	0.3%

[1] Number of eligible prescribers completing the survey (See Table 1).
[2] Categorization scheme of the verbatim responses is shown in Appendix B, Listing 3.
[3] Each category is only counted once per prescriber.

Prescribers and their experience with prescribing TIRF medicines are summarized in Table 6. Nearly half of the prescribers (46.7%) prescribed TIRF medicines 1 to 2 times a month within the past 6 months, and Actiq or generic Actiq was the most frequently prescribed TIRF medicine (79.6% of prescribers). Seventeen (17) prescribers indicated that they prescribed Onsolis during the 6 months prior to taking the survey, which would be after 11 March 2012. However, Onsolis was not available to any pharmacy at that time. Therefore, none of these prescription could have been filled. The last Onsolis provided to patients was in May 2011.

Table 6. Characteristics of Respondents Completing the Survey

Question	Eligible Completed Prescribers N=302[1]	
	n	%
Question 26: On average, how many times per month have you prescribed the TIRF medicines within the last 6 months		
None	42	13.9
1-2 times per month	141	46.7
3-5 times per month	71	23.5
More than 5 times per month	37	12.3
I don't remember	11	3.6
Question 27: Please select the TIRF medicines that you have prescribed within the last 6 months (select all that apply):[2]		
Abstral®	16	6.2
Actiq® or generic Actiq®	207	79.6
Fentora®	152	58.5
Lazanda®	24	9.2
Onsolis®	17	6.5
Subsys®	49	18.8
N/A (answered ***None*** to Question 26)	42	

[1] Number of eligible prescribers 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.

5.1.3 TIRF Medicines Educational Materials

Prescribers were asked about their awareness of educational materials for TIRF medicines, specifically the Full Prescribing Information, the Medication Guide, and the Patient-Prescriber

Agreement Form (PPAF) (Table 7). Most respondents had received or had access to the Full Prescribing Information and the Medication Guide (94.4% and 90.4%, respectively). Of those with access to these materials, 80.0% and 89.0%, respectively, indicated that they had read the Full Prescribing Information and the Medication Guide. Additionally, most prescribers reported reviewing the PPAF with each patient or their caregiver (88.1%); signing the PPAF and having the patient/caregiver sign the PPAF (94.0%); and giving a copy of the PPAF to the patient (82.5%).

Table 7. Responses to Questions About TIRF Medicines Educational Materials and the TIRF Patient-Prescriber Agreement Form

Question	Eligible Completed Prescribers N=302[1]	
	n	%
Question 17: Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine that you prescribe?		
Yes	285	94.4
No	7	2.3
I don't know	10	3.3
Question 18: Did you read the Full Prescribing Information for the TIRF medicine that you prescribe?[2]		
Yes	228	80.0
No	47	16.5
I don't know	10	3.5
N/A (answered ***No*** or ***I don't know*** to Question 17)	17	
Question 19: Did you receive or do you have access to the Medication Guide for the TIRF medicine that you prescribe?		
Yes	273	90.4
No	9	3.0
I don't know	20	6.6

(continued)

Table 7. Responses to Questions About TIRF Medicines Educational Materials and the TIRF Patient-Prescriber Agreement Form

Question 20: Did you read the Medication Guide for the TIRF medicine that you prescribe?[2]		
Yes	243	89.0
No	22	8.1
I don't know	8	2.9
N/A (answered ***No*** or ***I don't know*** to Question 19)	29	
Question 21: Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?		
Yes[3]	31	10.3
No	253	83.8
I don't know	18	6.0
Question 23: Do you review the Patient-Prescriber Agreement Form with each of your patients for whom you prescribe TIRF medicines or their caregiver?		
Yes	266	88.1
No	26	8.6
I don't know	10	3.3
Question 24: 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?[2]		
Yes	250	94.0
No	10	3.8
I don't know	6	2.3
N/A (answered ***No*** or ***I don't know*** to Question 23)	36	
Question 25: Do you give a copy of the Patient-Prescriber Agreement Form for TIRF medicines to the patient or their caregiver?		
Yes	249	82.5
No	35	11.6
I don't know	18	6.0

[1] Number of eligible prescribers 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 are presented in Appendix B, Listing 1.

There were 31 respondents who typed a response into the free text field for Question 21. These responses are categorized in Table 8 (see verbatim responses shown in Appendix B, Listing 1). There were 3 questions about dose titration (1.0%) and 2 questions each about indication and request for additional education (0.7%). Eight (8) of the responses were categorized as "general responses" (2.6%) and were primarily statements that questions had already been answered, or that respondents had no questions at the time of the survey.

Table 8. Categorized Responses To Question 22 (Questions about the Information in the Full Prescribing Information or Medication Guide)

Response (Categorized Type) [2]	Eligible Completed Prescribers N=302[1]	
	n [3]	%
Bioavailability	1	0.3%
Dose modifications	1	0.3%
Dose titration, Treatment failure	1	0.3%
Drug interactions	1	0.3%
Formulary, Insurance coverage	1	0.3%
Insurance coverage	1	0.3%
Metabolism	1	0.3%
Patient compliance monitoring	1	0.3%
Prescribing Information/Medication Guide access	1	0.3%
Request for Prescribing Information/Medication Guide	2	0.6%
Request for Prescribing Information/Medication Guide, REMS enrollment	1	0.3%
Simplification of Prescribing Information/Medication Guide	1	0.3%
TIRF medicine equivalences, Absorption	1	0.3%
TIRF medicine conversion, Insurance coverage	1	0.3%
Indication	2	0.7%
Request for additional education	2	0.7%
Dose titration	3	1.0%
General responses (specific questions not asked)	8	2.6%

[1] Number of eligible prescribers completing the survey (See Table 1).
[2] Categorization scheme of the verbatim responses is shown in Appendix B, Listing 1.
[3] Each category is only counted once per prescriber.

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 subgroup are described in a separate section of the document, Section 5.2.3.

5.2.1.1 Key Risk Message 1

Key Risk Message 1 assesses the prescriber's knowledge of the specific contraindications for TIRF medicines in patients.

Analysis of responses to components of Question 6 for Key Risk Message 1 showed that a high percentage of prescribers know that TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur (87.4%) and that death has occurred in opioid non-tolerant patients treated with some fentanyl products (95.7%). Most prescribers were aware patients just starting a TIRF medicine must begin with titration from the lowest available dose for that product (83.1%) and that TIRF medicines may not be used to treat opioid non-tolerant patients (82.5%), (Table 9). This is further supported by an average number of correct responses of 3.5 out of 4.

Table 9. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible Completed Prescribers N=302[1]	
	n	% (95% CI)[3]
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.		
6a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True[2]	264	87.4 (83.1, 90.9)
False	35	11.6
I don't know	3	1.0
6b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True[2]	289	95.7 (92.8, 97.7)
False	4	1.3
I don't know	9	3.0

(continued)

Table 9. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible Completed Prescribers N=302[1]	
	n	% (95% CI)[3]
6c: TIRF medicines may be used to treat opioid non-tolerant patients.		
True	45	14.9
False[2]	249	82.5 (77.7, 86.6)
I don't know	8	2.6
6d: 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]	251	83.1 (78.4, 87.2)
False	45	14.9
I don't know	6	2.0
Secondary Analysis: Demonstrated Understanding		
0 correct responses	1	0.3
1 correct response	9	3.0
2 correct responses	27	8.9
3 correct responses	70	23.2
4 correct responses	195	64.6
Average number of correct responses	3.5	(3.3, 4.0)[4]

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

[2] Indicates the correct response(s) to each question or item 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 assesses the prescriber's knowledge of the approved indications for prescribing TIRF Medicines to opioid tolerant patients.

Responses to components of Question 8 for Key Risk Message 2 indicate that a high percentage of prescribers were aware TIRF medicines are prescribed for adult opioid-tolerant patients with breakthrough pain from cancer (95.4%) and not for patients with acute or

postoperative pain (86.4%), headache or migraine pain (86.8%),or dental pain (96.0%), (Table 10). This is further supported by an average number of correct responses of 3.6 out of 4.

Table 10. 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=302[1]	
	n	% (95% CI) [3]
Question 8: 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.		
8a: Acute or postoperative pain		
Yes	38	12.6
No[2]	261	86.4 (82.0, 90.1)
I don't know	3	1.0
8b: Headache or migraine pain		
Yes	38	12.6
No[2]	262	86.8 (82.4, 90.4)
I don't know	2	0.7
8c: Dental pain		
Yes	7	2.3
No[2]	290	96.0 (93.2, 97.9)
I don't know	5	1.7
8d: Breakthrough pain from cancer		
Yes [2]	288	95.4 (92.3, 97.4)
No	14	4.6
I don't know	0	0.0

(continued)

Table 10. 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=302[1]	
	n	% (95% CI)[3]
Secondary Analysis: Demonstrated Understanding		
0 correct responses	0	0.0
1 correct response	7	2.3
2 correct responses	16	5.3
3 correct responses	54	17.9
4 correct responses	225	74.5
Average number of correct responses	3.6	(3.5, 4.0)[4]

[1] Number of eligible prescribers completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or item 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 assesses the prescriber's knowledge of the risk factors and signs and symptoms of opioid abuse in patients who take TIRF medicines.

Responses to components of Questions 6, 7, and 9 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 (99.7%), a personal history of psychiatric illness is a risk factor for opioid abuse (82.5%), 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 (99.3%), and that TIRF medicines can be abused in a manner similar to other opioid agonists (97.7%), (Table 11). This is further supported by an average number of correct responses of 3.8 out of 4.

Table 11. 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=302[1]	
	n	% (95% CI) [3]
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.		
6e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True [2]	301	99.7 (98.2, 100.0)
False	1	0.3
I don't know	0	0.0
Question 7: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.		
7a: A personal history of psychiatric illness		
Yes [2]	249	82.5 (77.7, 86.6)
No	37	12.3
I don't know	16	5.3
7b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes [2]	300	99.3 (97.6, 99.9)
No	1	0.3
I don't know	1	0.3
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.		
9a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True[2]	295	97.7 (95.3, 99.1)
False	6	2.0
I don't know	1	0.3

(continued)

Table 11. 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=302[1]	
	n	% (95% CI) [3]
Secondary Analysis: Demonstrated Understanding		
0 correct responses	0	0.0
1 correct response	0	0.0
2 correct responses	3	1.0
3 correct responses	57	18.9
4 correct responses	242	80.1
Average number of correct responses	3.8	(3.6, 4.0) [4]

[1] Number of eligible prescribers completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or item 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 assesses the prescriber's knowledge that TIRF medicines are not interchangeable regardless of the route of administration. .

Responses to components of Question 9 for Key Risk Message 4 showed that a high percentage of prescribers understood TIRF medicines are not interchangeable with each other regardless of the route of administration (95.7%), the conversion of 1 TIRF medicine to another may result in a fatal overdose (94.7%), and dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (90.4%), (Table 12). This is further supported by an average number of correct responses of 2.8 out of 3.

Table 12. 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=302[1]	
	n	% (95% CI)
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.		
9b: TIRF medicines are interchangeable with each other regardless of route of administration.		
True	9	3.0
False[2,3]	289	95.7 (92.8, 97.7)
I don't know	4	1.3
9c: 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[2,3]	286	94.7 (91.5, 96.9)
False	5	1.7
I don't know	11	3.6
9d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True[2,3]	273	90.4 (86.5, 93.5)
False	12	4.0
I don't know	17	5.6
Secondary Analysis: Demonstrated Understanding		
0 correct responses	3	1.0
1 correct response	7	2.3
2 correct responses	35	11.6
3 correct responses	257	85.1
Average number of correct responses [4]	2.8	(2.6, 3.0)

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

[2] Indicates the correct response(s) to each question or item 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 prescribers' responses to additional questions about the safety of TIRF medicines beyond those associated with the key risk messages. Responses to the additional questions listed in Table 14 confirmed the prescribers' understanding of the safety and the risks of taking TIRF medicines.

More than half of the prescribers (54.3%) correctly indicated TIRF medicines cannot be prescribed for chronic non-cancer pain; however, 44.4% indicated that they do prescribe TIRF medicines for chronic non cancer pain. The majority of prescribers correctly answered that a TIRF medicine for breakthrough pain is indicated for an adult patient with advanced lung cancer currently receiving fentanyl for cancer pain (85.1%), for an adult patient with advanced prostate cancer currently receiving morphine for bone metastasis (80.5%), an adult patient with advanced sarcoma currently taking hydromorphone (70.2%). Over 50% of responders correctly indicated that a TIRF medicine for breakthrough pain is not indicated for an adult patient with localized breast cancer following mastectomy (54.3%).

The majority of prescribers knew when switching the patient to a different TIRF medicine, they could not safely convert to the equivalent dosage of the new TIRF medicine (88.7%), they must not convert from the equivalent TIRF medicine dose to another TIRF medicine because this could result in fentanyl overdose (75.5%), they must not convert to the new TIRF medicine at half the dose (62.9%), or base the starting dose of the newly prescribed TIRF medicine on the dose of the opioid medicine used for underlying persistent cancer pain (57.9%).

Additionally, most prescribers correctly indicated that for a patient starting titration with a TIRF medicine, an appropriate dose is not based on the dose of opioid medicine used for underlying persistent cancer pain (62.9%), the dose is not based on the prescribers assessment based on their clinical experience (79.5%), or the median available dose (94.0%), and is based on the lowest available dose, unless the Full Prescribing Information provides specific guidance (91.4%). Many prescribers also knew that taking erythromycin, a CYP3A4 inhibitor, at the same time as a TIRF medication is allowed (54.6%), and the majority understood that use of a TIRF inhibitor with erythromycin may require dosage adjustment and the patient needs to be carefully monitored for opioid toxicity, otherwise such use may be fatal (86.6%), and there is the possibility of drug interaction between CYP3A4 inhibitors and TIRF medicines (81.1%). Less than half (40.7%) correctly identified that the dose of the TIRF medicine should not be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

Finally, a high percentage of prescribers correctly indicated TIRF medicines contain fentanyl in an amount that could be fatal to children and those who are not opioid tolerant (99.0%), that they should inform patients that TIRF medicines must not be used for any short term pain (91.7%), that if patients stop taking their around-the-clock opioid medicine they cannot continue to take their TIRF medicine (68.5%), and that they instruct patients never to share their TIRF medicine with anyone else (99.3%).

Despite the high proportion of prescribers responding correctly to the questions around Key Risk Message 1 (i.e., that patients must be opioid tolerant), only 7.9% of prescribers correctly indicated that patients considered opioid tolerant are those who are taking regular opioid therapy for 1 week or longer. Additionally, 15.6% correctly indicated that patients not currently taking opioid therapy but who have no known intolerance or hypersensitivity to fentanyl are not considered opioid tolerant. In contrast a high percentage (88.7%) correctly indicated patients not currently taking opioid therapy but who had taken opioid therapy before are not considered opioid tolerant.

Because the results to Question 5 are discrepant from the other prescriber results around opioid tolerance, it is possible that these results reflect a misunderstanding of the question rather than a lack of understanding of the important safety information. Additional research will be conducted to explore prescribers' interpretation and understanding of all 3 components of Question 5. The outcome of the research will be included in the next assessment report, and based on the outcome appropriate action may be taken, such as rephrasing Question 5.

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

Question	Eligible Completed Prescribers N=302[1]	
	n	%
Question 5: Please answer "True," "False," or "I don't know" for each of the following. According to the labeling, patients considered opioid-tolerant are those:		
5a: Who are taking regular opioid therapy for underlying persistent cancer pain for one week or longer.		
True [2]	24	7.9
False	271	89.7
I don't know	7	2.3
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before.		
True	25	8.3
False[2]	268	88.7
I don't know	9	3.0

(continued)

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

Question	Eligible Completed Prescribers N=302[1]	
	n	%
5c: Who are not currently taking opioid therapy, but with no known intolerance or hypersensitivity to the drug fentanyl.		
True	251	83.1
False[2]	47	15.6
I don't know	4	1.3
Question 7: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.		
7c: A family history of asthma		
Yes	20	6.6
No[2]	268	88.7
I don't know	14	4.6
Question 8: 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.		
8e: Chronic non-cancer pain		
Yes	134	44.4
No[2]	164	54.3
I don't know	4	1.3
Question 11: The following patients described are experiencing breakthrough pain. According to the labelling, a TIRF medicine is not appropriate for one of them. Please answer "Yes," "No," or "I don't know" as to whether each patient should receive a TIRF medicine.		
11a: Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.		
Yes[2]	257	85.1
No	38	12.6
I don't know	7	2.3

(continued)

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

Question	Eligible Completed Prescribers N=302[1]	
	n	%
11b: 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.		
Yes	126	41.7
No[2]	164	54.3
I don't know	12	4.0
11c: 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.		
Yes[2]	243	80.5
No	51	16.9
I don't know	8	2.6
11d: Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.		
Yes[2]	212	70.2
No	79	26.2
I don't know	11	3.6
Question 12: A patient is already taking a TIRF medicine but wants to change their medicine. The doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. How should the prescriber proceed? For each of the following scenarios, please indicate if it is a correct action for the prescriber by answering "Yes," "No," or "I don't know."		
12a: The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.		
Yes	25	8.3
No[2]	268	88.7
I don't know	9	3.0

(continued)

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

Question	Eligible Completed Prescribers N=302[1]	
	n	%
12b: The prescriber must not convert from the equivalent TIRF medicine dose to another TIRF medicine because they have different absorption properties and this could result in a fentanyl overdose.		
Yes[2]	228	75.5
No	66	21.9
I don't know	8	2.6
12c: Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.		
Yes	84	27.8
No[2]	190	62.9
I don't know	28	9.3
12d: 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.		
Yes	114	37.7
No[2]	175	57.9
I don't know	13	4.3
Question 13: A patient is starting titration with a TIRF medicine. What dose must they start with? Please indicate "Yes," "No," or "I don't know" for each of the following dosing scenarios.		
13a: An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.		
Yes	100	33.1
No[2]	190	62.9
I don't know	12	4.0
13b: The dose that the prescriber believes is appropriate based on their clinical experience.		
Yes	56	18.5
No[2]	240	79.5
I don't know	6	2.0

(continued)

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

Question	Eligible Completed Prescribers N=302[1]	
	n	%
13c: The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.		
Yes[2]	276	91.4
No	19	6.3
I don't know	7	2.3
13d: The median available dose.		
Yes	8	2.6
No[2]	284	94.0
I don't know	10	3.3
Question 15: A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please select "True," "False," or "I don't know" for each of the following statements.		
15a: The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.		
True	52	17.2
False[2]	165	54.6
I don't know	85	28.1
15b: 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.		
True[2]	262	86.8
False	11	3.6
I don't know	29	9.6
15c: There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.		
True	8	2.6
False[2]	245	81.1
I don't know	49	16.2

(continued)

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

Question	Eligible Completed Prescribers N=302[1]	
	n	%
15d: The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.		
True	71	23.5
False[2]	123	40.7
I don't know	108	35.8
Question 16: 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 counselling statements.		
16a: 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[2]	299	99.0
False	1	0.3
I don't know	2	0.7
16b: 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[2]	277	91.7
False	16	5.3
I don't know	9	3.0
16c: Instruct patients that, if they stop taking their around -the-clock opioid medicine, they can continue to take their TIRF medicine.		
True	63	20.9
False[2]	207	68.5
I don't know	32	10.6

(continued)

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

Question	Eligible Completed Prescribers N=302[1]	
	n	%
16d: Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.		
True[2]	300	99.3
False	1	0.3
I don't know	1	0.3

[1] Number of eligible prescribers completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or item within a question.

Responses to questions on managing breakthrough pain that is not sufficiently relieved are provided in Table 14. In the TIRF REMS Prescriber educational materials, this question is asked with a choice to select the best option in multiple choice format However, due to the logistics of conducting a survey via telephone administration, this question required a "yes," "no," or "I don't know" response for each question and did not permit the respondent to compare the response options to each other to identify the best answer. The responses to Question 14 in Table 14 are not assessed as correct or incorrect because the correct or incorrect answer depends on the prescribing information for the particular TIRF medicine.

The majority of prescribers indicated that when a patient has started titration of the lowest dose of a TIRF medicine and after 30 minutes breakthrough pain has not been sufficiently relieved, they would not advise the patient to take another identical dose of the TIRF medicine immediately (65.9%), to take a dose of an alternative rescue medicine (76.8%), or to double the dose and take immediately (96.0%). The minority of prescribers responded they should not provide guidance based on the product specific Medication Guide because the instructions are not the same for each TIRF medicine (7.0%).

When these questions are presented based on TIRF medicine prescribed, no trends in responses are evident (see Table 3-3, Appendix B).

Table 14. Responses to All Questions About What to Advise if Breakthrough Pain is Not Sufficiently Relieved

Question	Eligible Completed Prescribers N=302[1]	
	n	%
Question 14: 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 answer "Yes," "No," or "I don't know" for each of the scenarios described.		
14a: Take another (identical) dose of the TIRF medicine immediately.		
Yes	91	30.1
No	199	65.9
I don't know	12	4.0
14b: Take a dose of an alternative rescue medicine.		
Yes	59	19.5
No	232	76.8
I don't know	11	3.6
14c: Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.		
Yes	273	90.4
No	21	7.0
I don't know	8	2.6
14d: Double the dose and take immediately.		
Yes	4	1.3
No	290	96.0
I don't know	8	2.6

[1] 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 15).

More than half of prescribers indicated they always ask patients (or their caregivers) about the presence of children in the home (57.9%), instruct patients (or their caregivers) not to share TIRF medicines (79.1%), counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal (65.9%), instruct patients (or their caregivers) to keep

TIRF medicines out of the reach of children (72.8%), instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines (60.9%).

Less than half of prescribers (40.4%) always give patients (or their caregivers) the Medication Guide for their TIRF medicine, but 42.4% give their patients (or their caregivers) the Medication Guide for their TIRF medicine with the first prescription.

Table 15. Responses to All Questions About Activities When Prescribing TIRF Medicines

Question	Eligible Completed Prescribers N=302[1]	
	n	%
Question 10: 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."		
10a: Ask patients (or their caregivers) about the presence of children in the home.		
Always	175	57.9
Only with the first prescription	76	25.2
Sometimes	44	14.6
Never	5	1.7
I don't know	2	0.7
10b: Instruct patients (or their caregivers) not to share TIRF medicines with anyone else.		
Always	239	79.1
Only with the first prescription	36	11.9
Sometimes	24	7.9
Never	1	0.3
I don't know	2	0.7
10c: Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal.		
Always	199	65.9
Only with the first prescription	59	19.5
Sometimes	34	11.3
Never	8	2.6
I don't know	2	0.7

(continued)

Table 15. Responses to All Questions About Activities When Prescribing TIRF Medicines

Question	Eligible Completed Prescribers N=302[1]	
	n	%
10d: Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure.		
Always	220	72.8
Only with the first prescription	51	16.9
Sometimes	25	8.3
Never	4	1.3
I don't know	2	0.7
10e: Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines.		
Always	184	60.9
Only with the first prescription	75	24.8
Sometimes	37	12.3
Never	4	1.3
I don't know	2	0.7
10f: Give patients (or their caregivers) the Medication Guide for their TIRF medicine.		
Always	122	40.4
Only with the first prescription	128	42.4
Sometimes	28	9.3
Never	20	6.6
I don't know	4	1.3

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

5.2.3 Analyses of Subpopulations

To further assess prescriber understanding of key risk messages, subgroup analyses as described in Section 4.1.2 were conducted. All results are similar to the results in the primary population, and no trends are evident. The full set of subgroup 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=358), no prescribers reported an adverse event, product complaint, and/or medical information request associated with the use of TIRF medicines during phone completions of this survey. Twenty-one (21) reports of product complaints, and/or medical information requests were reported in the free text fields of surveys completed online by prescribers (Table 16; Appendix B, Listing 2). Adverse event, product complaint, or medical information request reports were categorized as described in Table 17.

Table 16. Respondent Report of Adverse Event, Product Complaint, or Medical Information Request During Survey

Question	All Respondents N=358[1]	
	n	%
Respondent spontaneously reported an adverse event, product complaint, or medical information request during the course of this survey.		
Yes[2]	21	5.9
No	337	94.1

[1] All respondents who took the survey regardless of eligibility.
[2] Verbatim text of adverse events, product complaints, or medical information requests is given in Appendix B, Listing 2.

Table 17. Categorized Reported Adverse Events, Product Complaints, or Medical Information Requests

Response (Categorized Type) [2]	All Respondents N=358[1]	
	n [3]	%
Adverse Event	0	0
Product Complaint	1	0.3%
Medical Information Request	20	5.6%

[1] All respondents who took the survey regardless of eligibility.
[2] Categorization scheme of the verbatim responses is shown in Appendix B, Listing 2.
[3] Each category is only counted once per prescriber.

5.4 Discussion, Conclusions, and Recommendations

The specific goals of the TIRF medicines prescriber KAB survey were to assess prescriber understanding of the risks associated with TIRF medicine use, of the specific indications for

treatment with TIRF medicines, that TIRF medicines are contraindicated in opioid non-tolerant patients.

Of the 5330 prescribers invited to participate, a total of 302 prescribers met eligibility criteria and completed the survey. The majority of respondents were male (59.6%). Respondents from the South, West, and Northeast included 31.1%, 26.8%, and 25.2% of the respondents, respectively; while respondents from the Midwest regions of the US composed 16.9%, of the total survey population. The most common healthcare degree was an MD (57.0%), and the most common medical specialties were pain management (50.7%) and oncology (22.5%). Of respondents who were medical doctors, half of the respondents (50.7%) had practiced medicine for more than 15 years.

Most respondents received or had access to the Full Prescribing Information and the Medication Guide (94.4% and 90.4%, respectively). Of those with access to these materials, 80.0% and 89.0%, respectively, claimed to have read the Full Prescribing Information and the Medication Guide. Additionally, most prescribers review the Patient-Prescriber Agreement Form with each patient or their caregiver (88.1%), and following review; the majority of those prescribers (94.0%) sign and have the patient/caregiver sign the form, and 82.5% give a copy of the Patient-Prescriber Agreement Form to the patient or their caregiver.

There were 4 key risk messages included in the survey. Prescriber demonstrated a high level of understanding of the 4 key risk messages, as there was a correct response rate of greater than 82% for all components of the key risk message questions.

Analysis of responses to Key Risk Message 1 showed that a high percentage of prescribers know that TIRF medicines are contraindicated in opioid non-tolerant patients (87.4%) and that death has occurred in opioid non-tolerant patients treated with some fentanyl products (95.7%). Most prescribers were aware that patients just starting a TIRF medicine must begin with titration from the lowest available dose for that product (83.1%) and that TIRF medicines may not be used to treat opioid non-tolerant patients (82.5%).

Responses to Key Risk Message 2 indicate that a high percentage of prescribers were aware TIRF medicines are prescribed for adult opioid-tolerant patients with breakthrough pain from cancer (95.4%) and not for patients with acute or postoperative pain (86.4%), headache or migraine pain (86.8%), or dental pain (96.0%).

Responses to 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 (99.7%), a personal history of psychiatric illness is a risk factor for opioid abuse (82.5%), 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 (99.3%), and that TIRF medicines can be abused in a manner similar to other opioid agonists (97.7%).

Responses to Key Risk Message 4 showed that a high percentage of prescribers understood TIRF medicines are not interchangeable with each other regardless of the route of administration (95.7%), the conversion of one TIRF medicine to another may result in a fatal

overdose (94.7%), and dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (90.4%).

Additional analyses of the key risk messages did not demonstrate any notable differences between subgroups of prescribers and no trends were evident.

Among responses to all questions about the safe use of TIRF medicines, there were 2 questions relating to the definition of a non-opioid tolerant patient that had low response rates. Despite the high proportion of prescribers responding correctly to the questions around Key Risk Message 1 (i.e., that patients must be opioid tolerant), only 7.9% of prescribers correctly indicated that patients considered opioid tolerant are those who are taking regular opioid therapy for 1 week or longer. In addition, 15.6% correctly indicated that patients not currently taking opioid therapy but who have no known intolerance or hypersensitivity to fentanyl are not considered opioid tolerant. Because the results to Question 5 are discrepant from the other prescriber results around opioid tolerance (e.g., Questions 6a, 6b, and 6c), it is possible that these results reflect a misunderstanding of the question rather than a lack of understanding of the important safety information. Additional research will be conducted to explore prescribers' interpretation and understanding of all 3 components of Question 5. The outcome of the research will be included in the next assessment report, and appropriate action may be taken based on the outcome.

Across the 4 key risk messages, prescribers demonstrated a high level of understanding 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 regardless of route of administration.

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)** **Archimedes Pharma US Inc.** **Cephalon, Inc.** **Endo Pharmaceuticals Inc.** **Insys Therapeutics** **Meda Pharmaceuticals** **Mallinckrodt (a Covidien Company)** **Par Pharmaceutical, Inc.** **ProStrakan, Inc.** **Sandoz, Inc.**
VERSION:	**3.0**
DATE:	**10 SEP 2012**
APPROVED:	**07 SEP 2012**

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LIST OF APPENDICES

1. LIST OF ABBREVIATIONS

CATI	Computer-Assisted Telephone Interviewing
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
ISI	Important Safety Information
KAB	Knowledge, Attitudes and Behavior
REALM	Rapid Estimate of Adult Literacy in Medicine
REMS	Risk Evaluation and Mitigation Strategy
SERP	Safety Event Reporting Plan
TIRF	Transmucosal Immediate Release Fentanyl
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation

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 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 REMS Industry Group (TRIG) includes Archimedes Pharma US Inc., Cephalon, Inc., Endo Pharmaceuticals Inc., Insys Therapeutics, Meda Pharmaceuticals, Mallinckrodt (a Covidien Company), Par Pharmaceutical, Inc., ProStrakan, Inc., and Sandoz Inc.

The Food and Drug Administration (FDA) has determined that a 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 Food and Drug Administration (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 bythe 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 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 first 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 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**
6	Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.	
6a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**TRUE**
6b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	**TRUE**
6c	TIRF medicines may be used to treat opioid non-tolerant patients.	**FALSE**
6d	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**
8	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.	
8a	Acute or postoperative pain	**NO**
8b	Headache or migraine pain	**NO**
8c	Dental pain	**NO**
8d	Breakthrough pain from cancer	**YES**

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**
6	Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.	
6e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**TRUE**
7	Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.	
7a	A personal history of psychiatric illness	**YES**
7b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**YES**
9	Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.	
9a	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**
9	Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.	
9b	TIRF medicines are interchangeable with each other regardless of route of administration.	**FALSE**
9c	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**
9d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**TRUE**

4.1.2 Additional Questions

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 : How frequently do you perform the following activities when prescribing TIRF medicines?
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.

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 BIf 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-respondents from the original sample with subsequent fax, e-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, except for prescribers from Vermont, Massachusetts, or Minnesota. Participants will be informed that prescribers from these states will not receive compensation for their participation. The mailing will include a Thank You Letter, the honorarium, 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 an 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 the first 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.

Precision of Estimated Rates of Understanding with a Sample Size of 300 (2-sided 95% Confidence Interval)

Estimated Rate of Understanding	Estimated Confidence Interval	
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 (this exclusion only applies to all subsequent waves).

- Prescribers or their immediate family members who have ever worked for Anesta LLC, Archimedes Pharma US Inc., Cephalon, Inc., Endo Pharmaceuticals Inc., Insys Therapeutics, Meda Pharmaceuticals, Mallinckrodt (a Covidien Company), Par Pharmaceutical, Inc., ProStrakan, Inc., Sandoz Inc., Teva Pharmaceuticals, Ltd., United BioSource Corporation, 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. 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 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 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 interviews.

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 respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents who complete the survey
- Representativeness of prescribers based on geography
- Description of survey participants, including:
  - 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

7.1.1 Description of Primary Analyses

Primary analyses are done for all key risk messages. 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.

7.1.2 Description of Secondary Analyses

Secondary analyses are done only for those key risk messages that contain multiple questions/items. 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.

7.1.3 Analysis Population

The analysis population will be based on eligible prescribers who completed the survey.

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, Product Complaint, or Medical Information Requests. 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 phone) 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 Reporting Plan (SERP). Additional detail regarding processes for adverse event reporting will be specified in the SERP.

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 needed 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 phone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by phone 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 phone 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.

- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines or a free-text response).

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 ONLINE/PHONE SURVEY CONTENT]

[PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl 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 Archimedes Pharma US Inc., Cephalon, Inc., Endo Pharmaceuticals Inc., Insys Therapeutics, Meda Pharmaceuticals, Mallinckrodt (a Covidien Company), Par Pharmaceutical, Inc., ProStrakan, and Sandoz 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.

[ONLINE ONLY]How We Use Your Information

[PHONE ONLY] 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 phone number will be used only if there are any questions about your survey responses.

[ONLINE ONLY] How We Protect Your Privacy

[PHONE ONLY]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.

[ONLINE ONLY] How to Learn More about This Survey

[ONLINE ONLY] 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.

[PHONE ONLY]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.

[ONLINE ONLY] Taking the Survey

[ONLINE ONLY] Once you have answered a question and moved on, you cannot go back and change your answers.

[ONLINE ONLY] Thank you for your participation in this survey.

[END 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 **[ONLY TERMINATE AFTER WAVE 1]**
   - ○ No
   - ○ I don't know **[ONLY TERMINATE AFTER WAVE 1]**

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]**
   - ○ Archimedes Pharma US Inc.**[TERMINATE]**
   - ○ Cephalon, Inc. **[TERMINATE]**
   - ○ Endo Pharmaceuticals Inc. **[TERMINATE]**
   - ○ Insys Therapeutics**[TERMINATE]**

- McKesson Specialty Care Solutions**[TERMINATE]**
- Mallinckrodt (a Covidien Company) **[TERMINATE]**
- Meda Pharmaceuticals **[TERMINATE]**
- Par Pharmaceutical, Inc.**[TERMINATE]**
- ProStrakan, Inc. **[TERMINATE]**
- Sandoz Inc. **[TERMINATE]**
- Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- RelayHealth**[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, patients considered opioid-tolerant are those:

	[RANDOMIZE LIST]	True	False	I don't know
5a.	Who are taking regular 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 are not currently taking opioid therapy, but with no known intolerance or hypersensitivity to the drug fentanyl	○	○	○

6. Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
6a.	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	○	○	○
6b.	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	○	○	○
6c.	TIRF medicines may be used to treat opioid non-tolerant patients.	○	○	○
6d.	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.	○	○	○
6e.	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	○	○	○

7. 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
7a.	A personal history of psychiatric illness	○	○	○
7b.	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	○	○	○
7c.	A family history of asthma	○	○	○

8. 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
8a.	Acute or postoperative pain	○	○	○
8b.	Headache or migraine pain	○	○	○
8c.	Dental pain	○	○	○
8d.	Breakthrough pain from cancer	○	○	○
8e.	Chronic non-cancer pain	○	○	○

9. Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
9a.	TIRF medicines can be abused in a manner similar to other opioid agonists.	○	○	○
9b.	TIRF medicines are interchangeable with each other regardless of route of administration.	○	○	○
9c.	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.	○	○	○
9d.	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	○	○	○

10. 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
10a.	Ask patients (or their caregivers) about the presence of children in the home	○	○	○	○	○
10b.	Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	○	○	○	○	○
10c.	Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	○	○	○	○	○
10d.	Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	○	○	○	○	○
10e.	Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	○	○	○	○	○
10f.	Give patients (or their caregivers) the Medication Guide for their TIRF medicine	○	○	○	○	○

11. The following patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Please answer "Yes," "No," or "I don't know" as to whether each patient should receive a TIRF medicine.

	[RANDOMIZE LIST]	Yes	No	I don't know
11a.	Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	○	○	○
11b.	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.	○	○	○
11c.	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.	○	○	○

11d.	Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	○	○	○

12. A patient is already taking a TIRF medicine but wants to change their medicine. The doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. How should the prescriber proceed? For each of the following scenarios, please indicate if it is a correct action for the prescriber by answering "Yes," "No," or "I don't know."

	[RANDOMIZE LIST]	**Yes**	**No**	**I don't know**
12a.	The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	○	○	○
12b.	The prescriber must not convert from the equivalent TIRF medicine dose to another TIRF medicine because they have different absorption properties and this could result in a fentanyl overdose.	○	○	○
12c.	Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	○	○	○
12d.	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.	○	○	○

13. A patient is starting titration with a TIRF medicine. What dose must they start with? Please indicate "Yes," "No," or "I don't know" for each of the following dosing scenarios.

	[RANDOMIZE LIST]	**Yes**	**No**	**I don't know**
13a.	An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.	○	○	○
13b.	The dose that the prescriber believes is appropriate based on their clinical experience.	○	○	○
13c.	The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.	○	○	○
13d.	The median available dose.	○	○	○

14. 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 answer "Yes," "No," or "I don't know" for each of the scenarios described.

	[RANDOMIZE LIST]	Yes	No	I don't know
14a.	Take another (identical) dose of the TIRF medicine immediately.	○	○	○
14b.	Take a dose of an alternative rescue medicine.	○	○	○
14c.	Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.	○	○	○
14d.	Double the dose and take immediately.	○	○	○

15. A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please select "True," "False," or "I don't know" for each of the following statements.

	[RANDOMIZE LIST]	True	False	I don't know
15a.	The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.	○	○	○
15b.	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.	○	○	○
15c.	There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.	○	○	○
15d.	The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.	○	○	○

16. 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**
16a.	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.	○	○	○
16b.	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.	○	○	○
16c.	Instruct patients that, if they stop taking their around - the-clock opioid medicine, they can continue to take their TIRF medicine.	○	○	○
16d.	Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.	○	○	○

[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.

17. Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine that you prescribe?

- ○ Yes
- ○ No **[GO TO Q19]**
- ○ I don't know **[GO TO Q19]**

18. Did you read the Full Prescribing Information for the TIRF medicine that you prescribe?

- ○ Yes
- ○ No
- ○ I don't know

19. Did you receive or do you have access to the Medication Guide for the TIRF medicine that you prescribe?

- ○ Yes
- ○ No **[GO TO Q21]**
- ○ I don't know **[GO TO Q21]**

20. Did you read the Medication Guide for the TIRF medicine that you prescribe?

- ○ Yes
- ○ No
- ○ I don't know

21. Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?

- ○ Yes
- ○ No **[GO TO Q23]**
- ○ I don't know **[GO TO Q23]**

22. What are your questions?**[MULTILINE INPUT]**

23. 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 Q25]**
- ○ I don't know **[GO TO Q25]**

24. 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

25. 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]

There are just a few more questions to help us combine your answers with other answers we have received.

26. 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

27. Please select the TIRF medicines that you have prescribed within the last 6 months: (select all that apply)

- ○ Abstral®
- ○ Actiq® or generic Actiq®
- ○ Fentora® or generic Fentora®
- ○ Lazanda®
- ○ Onsolis®
- ○ Subsys™

[DEMOGRAPHICS PREAMBLE 2]These last few questions are for demographic purposes.

28. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

29. What is your medical degree?

- ○ MD
- ○ DO
- ○ Nurse Practitioner **[Go to Q31]**
- ○ Physician Assistant **[Go to Q31]**
- ○ Prefer not to answer

30. In total, how many years have you been practicing medicine, since completing your post-graduate education?

- ○ Less than 3 years
- ○ 3 – 5 years
- ○ 6 – 10 years
- ○ 11 – 15 years
- ○ More than 15 years
- ○ Prefer not to answer

31. In which state do you practice?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" at END]

32. What is your medical specialty?

- ○ Oncology
- ○ Primary care
- ○ Pain management
- ○ Other (please specify): _____

[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: _____

LAST NAME: _____

ADDRESS: **[MULTILINE INPUT]**

CITY: _____

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: _____

[CLOSING 2]

We would also like to ask for your telephone number and NPI number. Providing your telephone number and NPI number is optional. Your telephone number 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 NPI NUMBER QUESTION]**

Telephone: _____

[NEW PAGE]

Do you want to provide your NPI number?

- ○ Yes
- ○ No **[SKIP TO CLOSING 3]**

NPI #: _____

[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 include Archimedes Pharma US Inc., Cephalon, Inc., Endo Pharmaceuticals Inc., Insys Therapeutics, Meda Pharmaceuticals, Mallinckrodt (a Covidien Company), Par Pharmaceutical, Inc., ProStrakan, Inc., and Sandoz Inc (collectively referred to as the "TIRF Industry REMS Group"). 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. 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.

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 10PM 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,

TIRF REMS Industry Group

* 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.

Appendix B Prescriber Survey Listings and Subanalysis Tables

Prescriber Listings

Listing 1 CATEGORIZATION OF VERBATIM RESPONSES TO QUESTION 22 (Questions about the information in the Full Prescribing Information or Medication Guide)

Verbatim Response	Categorized Response
Already answered by rep.	General response
Can they be simplified for quick read?	Simplification of Prescribing Information/Medication Guide
Clarification of some conversions, insurance coverage	TIRF medicine conversion, insurance coverage
Could I work with our palliative care doctors to come up with an "optimal" oral pain medication regimen prior to trying the TIRF medications?	General Question
Dosage changes for side effects	Dose modifications
Formulary questions Coverage	Formulary, Insurance coverage
Frequency, guidelines [sic] on possible drug interactions etc.	Drug interactions
Highlighted on this survey!	General response
How best to monitor patient compliance and efficacy of prescribed meds, taking into account dosing schedules, laboratory vagaries, comorbid conditions and potential interactions with newly added drugs in changing treatment protocols?	Patient compliance monitoring
How can I get a copy to keep on file in the office?	Request for Prescribing Information/Medication Guide
I had specific questions regarding escalating doses.	Dose titration
I need a confirmation email that I am a TIRF prescriber. Also, I would appreciate the info on all TIRF meds	Request for Prescribing Information/Medication Guide, REMS enrollment

Verbatim Response	Categorized Response
I need further education regarding the prescribing of these medications. I'm a primary care physician and I never initiate these medications. I have one patient on a long acting fentanyl. I never adjust her dosage but I feel I need more education regarding these medications.	Request for additional education
I often have questions about bioavailability	Bioavailability
I would like extra copies to keep at the nursing station	Request for Prescribing Information/Medication Guide
Is it appropriate in COPD	Indication
Metabolism	Metabolism
N/A	General response
None	General response
Questions regarding treatment failure and titration	Dose titration, treatment failure
Questions were already answered	General response
Rationale of using in chronic pain conditions.	Indication
Rep arranged for me to speak with someone from the company pharmacy department when I had a quest. I have no request now	General response
Rough equivalence of products. Absorption characteristics.	TIRF medicine equivalences, absorption
Titrating regimen	Dose titration
Titrations	Dose titration
Unclear	General response
Where can I access the medication guide?	Prescribing Information/Medication Guide access
Where can I find whether the medication will be covered readily?	Insurance coverage
Why have I not been made more aware of the TIRF options	Request for additional education

Listing 2 CATEGORIZATION OF VERBATIM RESPONSES TO REPORTED SAFETY EVENTS OR PRODUCT COMPLAINTS

Verbatim Response	Categorized Response
Can they be simplified for quick read?	Product complaint
Clarification of some conversions, insurance coverage	Medical information request
Could I work with our palliative care doctors to come up with an "optimal" oral pain medication regimen prior to trying the TIRF medications?	Medical information request
Dosage changes for side effects	Medical information request
Formulary questions Coverage	Medical information request
Frequency, guidelines on possible drug interactions etc.	Medical information request
How best to monitor patient compliance and efficacy of prescribed meds, taking into account dosing schedules, laboratory vagaries, comorbid conditions and potential interactions with newly added drugs in changing treatment protocols?	Medical information request
How can I get a copy to keep on file in the office?	Medical information request
I had specific questions regarding escalating doses.	Medical information request
I need a confirmation email that I am a TIRF prescriber. Also, I would appreciate the info on all TIRF meds	Medical information request
I need further education regarding the prescribing of these medications. I'm a primary care physician and I never initiate these medications. I have one patient on a long acting fentanyl. I never adjust her dosage but I feel I need more education regarding these medications.	Medical information request
I often have questions about bioavailability	Medical information request
I would like extra copies to keep at the nursing station	Medical information request

Verbatim Response	Categorized Response
Is it appropriate in COPD?	Medical information request
Metabolism	Medical information request
Rationale of using in chronic pain conditions.	Medical information request
Rough equivalence of products. Absorption characteristics.	Medical information request
Titrating regimen	Medical information request
Titrations	Medical information request
Where can I access the medication guide?	Medical information request
Where can I find whether the medication will be covered readily?	Medical information request

Listing 3 CATEGORIZATION OF VERBATIM RESPONSES TO QUESTION 33 (OTHER MEDICAL SPECIALTY)

Verbatim Response	Categorized Response
Hospice and Palliative Medicine	General Medicine
Neurology	Neurology
Palliative care	General Medicine
Palliative medicine	General Medicine
PM&R	Rehabilitation
Psychiatry	Psychiatry
Rheumatology	Rheumatology
Bone marrow transplant	Oncology - Hematology
Gyn oncology	Oncology - Gynecology
Emergency medicine	Emergency Medicine
Hospice & palliative medicine	General Medicine
Physical Medicine and Rehabilitation	Rehabilitation
Adult trauma	Emergency Medicine
Geriatric/Pain management	Gerontology
Physical medicine rehabilitation	Rehabilitation
Radiation oncology	Oncology - Radiology
General practice	General Medicine
Anesthesiology	Anesthesiology
PM&R/pain	Rehabilitation

Prescriber Subanalysis Tables

TABLE 3.3 RESPONSES TO THE QUESTION ABOUT WHAT TO ADVISE IF BREAKTHROUGH PAIN IS NOT SUFFICIENTLY RELIEVED BY TIRF MEDICINES PRESCRIBED

Question	Abstral® N=16		Actiq® or generic Actiq® N=207		Fentora® or generic Fentora® N=152		Lazanda® N=24		Onsolis® N=17		Subsys™ N=49		Fentora® or generic Fentora® and at least one additional TIRF medicine N=121		Onsolis®, Abstral®, and/or Lazanda® and at least one additional TIRF medicine N=37	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Question 14: 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 answer "Yes," "No," or "I don't know" for each of the scenarios described.																
14a: Take another (identical) dose of the TIRF medicine immediately.																
Yes	6	37.5	67	32.4	55	36.2	3	12.5	4	23.5	26	53.1	45	37.2	11	29.7
No	10	62.5	133	64.3	93	61.2	21	87.5	13	76.5	23	46.9	74	61.2	26	70.3
I don't know	0	0.0	7	3.4	4	2.6	0	0.0	0	0.0	0	0.0	2	1.7	0	0.0
14b: Take a dose of an alternative rescue medicine.																
Yes	6	37.5	42	20.3	26	17.1	6	25.0	8	47.1	14	28.6	22	18.2	11	29.7
No	10	62.5	159	76.8	122	80.3	18	75.0	8	47.1	35	71.4	98	81.0	25	67.6
I don't know	0	0.0	6	2.9	4	2.6	0	0.0	1	5.9	0	0.0	1	0.8	1	2.7

Question	Abstral® N=16		Actiq® or generic Actiq® N=207		Fentora® or generic Fentora® N=152		Lazanda® N=24		Onsolis® N=17		Subsys™ N=49		Fentora® or generic Fentora® and at least one additional TIRF medicine N=121		Onsolis®, Abstral®, and/or Lazanda® and at least one additional TIRF medicine N=37	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
14c: Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.																
Yes	14	87.5	187	90.3	138	90.8	23	95.8	16	94.1	41	83.7	110	90.9	34	91.9
No	2	12.5	12	5.8	9	5.9	1	4.2	1	5.9	5	10.2	6	5.0	3	8.1
I don't know	0	0.0	8	3.9	5	3.3	0	0.0	0	0.0	3	6.1	5	4.1	0	0.0
14d: Double the dose and take immediately.																
Yes	2	12.5	3	1.4	3	2.0	1	4.2	1	5.9	1	2.0	3	2.5	2	5.4
No	13	81.3	198	95.7	148	97.4	23	95.8	16	94.1	48	98.0	118	97.5	34	91.9
I don't know	1	6.3	6	2.9	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	1	2.7

Note: A Prescriber can prescribe more than one TIRF Medicines. Therefore, the number of prescribed TIRF Medicines may not sum up to the number of prescribers.

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 AND 20):

- **S-1a - Respondents who got read the Full Prescribing Information for the TIRF medicine that they prescribe , or who read the Medication Guide.**
- **S-1b - Respondents who did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 18) and did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 20).**

Question	S-1a Read Medication Guide or Prescribing Info N=263		S-1b Did not read Medication Guide or Prescribing Info N=39	
	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.				
6a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.				
Correct response				
True	231	87.8 (83.3, 91.5)	33	84.6 (69.5, 94.1)
Incorrect response				
False	29	11.0	6	15.4
I don't know	3	1.1	0	0.0
6b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.				
Correct response				
True	250	95.1 (91.7, 97.3)	39	100.0 (91.0, 100.0)
Incorrect response				
False	4	1.5	0	0.0
I don't know	9	3.4	0	0.0

Question	S-1a Read Medication Guide or Prescribing Info N=263		S-1b Did not read Medication Guide or Prescribing Info N=39	
	N	% (95% CI)	N	% (95% CI)
6c: TIRF medicines may be used to treat opioid non-tolerant patients.				
Correct response				
False	221	84.0 (79.0, 88.2)	28	71.8 (55.1, 85.0)
Incorrect response				
True	36	13.7	9	23.1
I don't know	6	2.3	2	5.1
6d: 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	220	83.7 (78.6, 87.9)	31	79.5 (63.5, 90.7)
Incorrect response				
False	37	14.1	8	20.5
I don't know	6	2.3	0	0.0

TABLE 6.2.1 SECONDARY 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 AND 20):

- **S-1a - Respondents who got read the Full Prescribing Information for the TIRF medicine that they prescribe, or who read the Medication Guide.**
- **S-1b - Respondents who did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 18) and did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 20).**

Demonstrated Understanding	S-1a Read Medication Guide or Prescribing Info N=263		S-1b Did not read Medication Guide or Prescribing Info N=39	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	1	0.4	0	0.0
1 correct response	7	2.7	2	5.1
2 correct responses	23	8.7	4	10.3
3 correct responses	59	22.4	11	28.2
4 correct responses	173	65.8	22	56.4
Average number of correct responses	3.5	(3.3, 4.0)	3.4	(2.9, 4.0)

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 AND 20):

- **S-1a - Respondents who got read the Full Prescribing Information for the TIRF medicine that they prescribe , or who read the Medication Guide.**
- **S-1b - Respondents who did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 18) and did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 20).**

Question	S-1a Read Medication Guide or Prescribing Info N=263		S-1b Did not read Medication Guide or Prescribing Info N=39	
	N	% (95% CI)	N	% (95% CI)
Question 8: 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.				
8a: Acute or postoperative pain				
Correct response				
No	229	87.1 (82.4, 90.9)	32	82.1 (66.5, 92.5)
Incorrect response				
Yes	32	12.2	6	15.4
I don't know	2	0.8	1	2.6

Question	S-1a Read Medication Guide or Prescribing Info N=263		S-1b Did not read Medication Guide or Prescribing Info N=39	
	N	% (95% CI)	N	% (95% CI)
8b: Headache or migraine pain				
Correct response				
No	234	89.0 (84.5, 92.5)	28	71.8 (55.1, 85.0)
Incorrect response				
Yes	28	10.6	10	25.6
I don't know	1	0.4	1	2.6
8c: Dental pain				
Correct response				
No	254	96.6 (93.6, 98.4)	36	92.3 (79.1, 98.4)
Incorrect response				
Yes	5	1.9	2	5.1
I don't know	4	1.5	1	2.6
8d: Breakthrough pain from cancer				
Correct response				
Yes	252	95.8 (92.6, 97.9)	36	92.3 (79.1, 98.4)
Incorrect response				
No	11	4.2	3	7.7
I don't know	0	0.0	0	0.0

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 AND 20):

- **S-1a - Respondents who got read the Full Prescribing Information for the TIRF medicine that they prescribe, or who read the Medication Guide.**
- **S-1b - Respondents who did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 18) and did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 20).**

Demonstrated Understanding	S-1a Read Medication Guide or Prescribing Info N=263		S-1b Did not read Medication Guide or Prescribing Info N=39	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0
1 correct response	4	1.5	3	7.7
2 correct responses	13	4.9	3	7.7
3 correct responses	45	17.1	9	23.1
4 correct responses	201	76.4	24	61.5
Average number of correct responses	3.7	(3.5, 4.0)	3.4	(2.9, 4.0)

TABLE 8.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

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 AND 20):

- **S-1a - Respondents who got read the Full Prescribing Information for the TIRF medicine that they prescribe , or who read the Medication Guide.**
- **S-1b - Respondents who did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 18) and did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 20).**

Question	S-1a Read Medication Guide or Prescribing Info N=263		S-1b Did not read Medication Guide or Prescribing Info N=39	
	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.				
6e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.				
Correct response				
True	262	99.6 (97.9, 100.0)	39	100.0 (91.0, 100.0)
Incorrect response				
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=263		S-1b Did not read Medication Guide or Prescribing Info N=39	
	N	% (95% CI)	N	% (95% CI)
Question 7: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.				
7a: A personal history of psychiatric illness				
Correct response				
Yes	218	82.9 (77.8, 87.2)	31	79.5 (63.5, 90.7)
Incorrect response				
No	33	12.5	4	10.3
I don't know	12	4.6	4	10.3
7b: 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	262	99.6 (97.9, 100.0)	38	97.4 (86.5, 99.9)
Incorrect response				
No	1	0.4	0	0.0
I don't know	0	0.0	1	2.6
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.				
9a: TIRF medicines can be abused in a manner similar to other opioid agonists.				
Correct response				
True	257	97.7 (95.1, 99.2)	38	97.4 (86.5, 99.9)
Incorrect response				
False	6	2.3	0	0.0
I don't know	0	0.0	1	2.6

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 AND 20):

- **S-1a - Respondents who got read the Full Prescribing Information for the TIRF medicine that they prescribe, or who read the Medication Guide.**
- **S-1b - Respondents who did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 18) and did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 20).**

Demonstrated Understanding	S-1a Read Medication Guide or Prescribing Info N=263		S-1b Did not read Medication Guide or Prescribing Info N=39	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0
2 correct responses	2	0.8	1	2.6
3 correct responses	49	18.6	8	20.5
4 correct responses	212	80.6	30	76.9
Average number of correct responses	3.8	(3.6, 4.0)	3.7	(3.2, 4.0)

TABLE 9.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

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 AND 20):

- **S-1a - Respondents who got read the Full Prescribing Information for the TIRF medicine that they prescribe, or who read the Medication Guide.**
- **S-1b - Respondents who did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 18) and did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 20).**

Question	S-1a Read Medication Guide or Prescribing Info N=263		S-1b Did not read Medication Guide or Prescribing Info N=39	
	N	% (95% CI)	N	% (95% CI)
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.				
9b: TIRF medicines are interchangeable with each other regardless of route of administration.				
Correct response				
False	253	96.2 (93.1, 98.2)	36	92.3 (79.1, 98.4)
Incorrect response				
True	7	2.7	2	5.1
I don't know	3	1.1	1	2.6
9c: 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	248	94.3 (90.8, 96.8)	38	97.4 (86.5, 99.9)
Incorrect response				
False	5	1.9	0	0.0
I don't know	10	3.8	1	2.6

Question	S-1a Read Medication Guide or Prescribing Info N=263		S-1b Did not read Medication Guide or Prescribing Info N=39	
	N	% (95% CI)	N	% (95% CI)
9d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.				
Correct response				
True	241	91.6 (87.6, 94.7)	32	82.1 (66.5, 92.5)
Incorrect response				
False	11	4.2	1	2.6
I don't know	11	4.2	6	15.4

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 AND 20):

- **S-1a - Respondents who got read the Full Prescribing Information for the TIRF medicine that they prescribe, or who read the Medication Guide.**
- **S-1b - Respondents who did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 18) and did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 20).**

Demonstrated Understanding	S-1a Read Medication Guide or Prescribing Info N=263		S-1b Did not read Medication Guide or Prescribing Info N=39	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	2	0.8	1	2.6
1 correct response	7	2.7	0	0.0
2 correct responses	27	10.3	8	20.5
3 correct responses	227	86.3	30	76.9
Average number of correct responses	2.8	(2.7, 3.0)	2.7	(2.3, 3.0)

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 29):

- **S-2a - MD**
- **S-2b - DO**
- **S-2c - Nurse Practitioner**
- **S-2d - Physician Assistant**

Question	S-2a MD N=172		S-2b DO N=26		S-2c Nurse Practitioner N=55		S-2d Physician Assistant N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
6a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.								
Correct response								
True	152	88.4 (82.6, 92.8)	21	80.8 (60.6, 93.4)	47	85.5 (73.3, 93.5)	41	89.1 (76.4, 96.4)
Incorrect response								
False	18	10.5	5	19.2	7	12.7	5	10.9
I don't know	2	1.2	0	0.0	1	1.8	0	0.0

Question	S-2a MD N=172		S-2b DO N=26		S-2c Nurse Practitioner N=55		S-2d Physician Assistant N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
6b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.								
Correct response								
True	167	97.1 (93.3, 99.0)	24	92.3 (74.9, 99.1)	49	89.1 (77.8, 95.9)	46	100.0 (92.3, 100.0)
Incorrect response								
False	1	0.6	1	3.8	2	3.6	0	0.0
I don't know	4	2.3	1	3.8	4	7.3	0	0.0
6c: TIRF medicines may be used to treat opioid non-tolerant patients.								
Correct response								
False	138	80.2 (73.5, 85.9)	22	84.6 (65.1, 95.6)	44	80.0 (67.0, 89.6)	42	91.3 (79.2, 97.6)
Incorrect response								
True	29	16.9	3	11.5	10	18.2	3	6.5
I don't know	5	2.9	1	3.8	1	1.8	1	2.2
6d: 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	142	82.6 (76.0, 87.9)	17	65.4 (44.3, 82.8)	47	85.5 (73.3, 93.5)	43	93.5 (82.1, 98.6)
Incorrect response								
False	25	14.5	8	30.8	8	14.5	3	6.5
I don't know	5	2.9	1	3.8	0	0.0	0	0.0

Table 6.2.2 SECONDARY 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 29):

- **S-2a - MD**
- **S-2b - DO**
- **S-2c - Nurse Practitioner**
- **S-2d - Physician Assistant**

Demonstrated Understanding	S-2a MD N=172		S-2b DO N=26		S-2c Nurse Practitioner N=55		S-2d Physician Assistant N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	1	0.6	0	0.0	0	0.0	0	0.0
1 correct response	6	3.5	1	3.8	2	3.6	0	0.0
2 correct responses	13	7.6	3	11.5	8	14.5	3	6.5
3 correct responses	41	23.8	11	42.3	11	20.0	6	13.0
4 correct responses	111	64.5	11	42.3	34	61.8	37	80.4
Average number of correct responses	3.5	(3.2, 4.0)	3.2	(2.7, 4.0)	3.4	(3.0, 4.0)	3.7	(3.3, 4.0)

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 29):

- **S-2a - MD**
- **S-2b - DO**
- **S-2c - Nurse Practitioner**
- **S-2d - Physician Assistant**

Question	S-2a MD N=172		S-2b DO N=26		S-2c Nurse Practitioner N=55		S-2d Physician Assistant N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 8: 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.								
8a: Acute or postoperative pain								
Correct response								
No	151	87.8 (81.9, 92.3)	22	84.6 (65.1, 95.6)	44	80.0 (67.0, 89.6)	42	91.3 (79.2, 97.6)
Incorrect response								
Yes	19	11.0	4	15.4	10	18.2	4	8.7
I don't know	2	1.2	0	0.0	1	1.8	0	0.0

Question	S-2a MD N=172		S-2b DO N=26		S-2c Nurse Practitioner N=55		S-2d Physician Assistant N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
8b: Headache or migraine pain								
Correct response								
No	149	86.6 (80.6, 91.3)	21	80.8 (60.6, 93.4)	49	89.1 (77.8, 95.9)	41	89.1 (76.4, 96.4)
Incorrect response								
Yes	21	12.2	5	19.2	6	10.9	5	10.9
I don't know	2	1.2	0	0.0	0	0.0	0	0.0
8c: Dental pain								
Correct response								
No	166	96.5 (92.6, 98.7)	25	96.2 (80.4, 99.9)	52	94.5 (84.9, 98.9)	44	95.7 (85.2, 99.5)
Incorrect response								
Yes	4	2.3	1	3.8	0	0.0	2	4.3
I don't know	2	1.2	0	0.0	3	5.5	0	0.0
8d: Breakthrough pain from cancer								
Correct response								
Yes	161	93.6 (88.8, 96.8)	25	96.2 (80.4, 99.9)	54	98.2 (90.3, 100.0)	45	97.8 (88.5, 99.9)
Incorrect response								
No	11	6.4	1	3.8	1	1.8	1	2.2
I don't know	0	0.0	0	0.0	0	0.0	0	0.0

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 29):

- **S-2a - MD**
- **S-2b - DO**
- **S-2c - Nurse Practitioner**
- **S-2d - Physician Assistant**

Demonstrated Understanding	S-2a MD N=172		S-2b DO N=26		S-2c Nurse Practitioner N=55		S-2d Physician Assistant N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	5	2.9	0	0.0	0	0.0	2	4.3
2 correct responses	7	4.1	2	7.7	6	10.9	0	0.0
3 correct responses	32	18.6	7	26.9	9	16.4	6	13.0
4 correct responses	128	74.4	17	65.4	40	72.7	38	82.6
Average number of correct responses	3.6	(3.4, 4.0)	3.6	(3.0, 4.0)	3.6	(3.2, 4.0)	3.7	(3.3, 4.0)

TABLE 8.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

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 29):

- **S-2a - MD**
- **S-2b - DO**
- **S-2c - Nurse Practitioner**
- **S-2d - Physician Assistant**

Question	S-2a MD N=172		S-2b DO N=26		S-2c Nurse Practitioner N=55		S-2d Physician Assistant N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
6e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.								
Correct response								
True	171	99.4 (96.8, 100.0)	26	100.0 (86.8, 100.0)	55	100.0 (93.5, 100.0)	46	100.0 (92.3, 100.0)
Incorrect response								
False	1	0.6	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-2a MD N=172		S-2b DO N=26		S-2c Nurse Practitioner N=55		S-2d Physician Assistant N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.								
7a: A personal history of psychiatric illness								
Correct response								
Yes	141	82.0 (75.4, 87.4)	24	92.3 (74.9, 99.1)	42	76.4 (63.0, 86.8)	39	84.8 (71.1, 93.7)
Incorrect response								
No	23	13.4	2	7.7	9	16.4	3	6.5
I don't know	8	4.7	0	0.0	4	7.3	4	8.7
7b: 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	172	100.0 (97.9, 100.0)	26	100.0 (86.8, 100.0)	54	98.2 (90.3, 100.0)	45	97.8 (88.5, 99.9)
Incorrect response								
No	0	0.0	0	0.0	1	1.8	0	0.0
I don't know	0	0.0	0	0.0	0	0.0	1	2.2

Question	S-2a MD N=172		S-2b DO N=26		S-2c Nurse Practitioner N=55		S-2d Physician Assistant N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
9a: TIRF medicines can be abused in a manner similar to other opioid agonists.								
Correct response								
True	168	97.7 (94.2, 99.4)	25	96.2 (80.4, 99.9)	55	100.0 (93.5, 100.0)	44	95.7 (85.2, 99.5)
Incorrect response								
False	4	2.3	0	0.0	0	0.0	2	4.3
I don't know	0	0.0	1	3.8	0	0.0	0	0.0

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 29):

- **S-2a - MD**
- **S-2b - DO**
- **S-2c - Nurse Practitioner**
- **S-2d - Physician Assistant**

Demonstrated Understanding	S-2a MD N=172		S-2b DO N=26		S-2c Nurse Practitioner N=55		S-2d Physician Assistant N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
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	1	1.8	2	4.3
3 correct responses	36	20.9	3	11.5	12	21.8	6	13.0
4 correct responses	136	79.1	23	88.5	42	76.4	38	82.6
Average number of correct responses	3.8	(3.5, 4.0)	3.9	(3.2, 4.0)	3.7	(3.3, 4.0)	3.8	(3.3, 4.0)

Table 9.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

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 29):

- **S-2a - MD**
- **S-2b - DO**
- **S-2c - Nurse Practitioner**
- **S-2d - Physician Assistant**

Question	S-2a MD N=172		S-2b DO N=26		S-2c Nurse Practitioner N=55		S-2d Physician Assistant N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
9b: TIRF medicines are interchangeable with each other regardless of route of administration.								
Correct response								
False	161	93.6 (88.8, 96.8)	24	92.3 (74.9, 99.1)	55	100.0 (93.5, 100.0)	46	100.0 (92.3, 100.0)
Incorrect response								
True	7	4.1	2	7.7	0	0.0	0	0.0
I don't know	4	2.3	0	0.0	0	0.0	0	0.0

Question	S-2a MD N=172		S-2b DO N=26		S-2c Nurse Practitioner N=55		S-2d Physician Assistant N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9c: 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	164	95.3 (91.0, 98.0)	23	88.5 (69.8, 97.6)	50	90.9 (80.0, 97.0)	46	100.0 (92.3, 100.0)
Incorrect response								
False	3	1.7	0	0.0	2	3.6	0	0.0
I don't know	5	2.9	3	11.5	3	5.5	0	0.0
9d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.								
Correct response								
True	156	90.7 (85.3, 94.6)	23	88.5 (69.8, 97.6)	46	83.6 (71.2, 92.2)	45	97.8 (88.5, 99.9)
Incorrect response								
False	9	5.2	0	0.0	3	5.5	0	0.0
I don't know	7	4.1	3	11.5	6	10.9	1	2.2

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 29):

- **S-2a - MD**
- **S-2b - DO**
- **S-2c - Nurse Practitioner**
- **S-2d - Physician Assistant**

Demonstrated Understanding	S-2a MD N=172		S-2b DO N=26		S-2c Nurse Practitioner N=55		S-2d Physician Assistant N=46	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	2	1.2	1	3.8	0	0.0	0	0.0
1 correct response	3	1.7	1	3.8	3	5.5	0	0.0
2 correct responses	23	13.4	3	11.5	8	14.5	1	2.2
3 correct responses	144	83.7	21	80.8	44	80.0	45	97.8
Average number of correct responses	2.8	(2.6, 3.0)	2.7	(2.2, 3.0)	2.7	(2.4, 3.0)	3.0	(2.6, 3.0)

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=49		S-3b 10 to <20 min N=172		S-3c >= 20 min N=72	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.						
6a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.						
Correct response						
True	42	85.7 (72.8, 94.1)	154	89.5 (84.0, 93.7)	61	84.7 (74.3, 92.1)
Incorrect response						
False	5	10.2	17	9.9	11	15.3
I don't know	2	4.1	1	0.6	0	0.0
6b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.						
Correct response						
True	47	95.9 (86.0, 99.5)	166	96.5 (92.6, 98.7)	67	93.1 (84.5, 97.7)
Incorrect response						
False	1	2.0	2	1.2	1	1.4
I don't know	1	2.0	4	2.3	4	5.6

Question	S-3a <10 min N=49		S-3b 10 to <20 min N=172		S-3c >= 20 min N=72	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
6c: TIRF medicines may be used to treat opioid non-tolerant patients.						
Correct response						
False	36	73.5 (58.9, 85.1)	144	83.7 (77.3, 88.9)	62	86.1 (75.9, 93.1)
Incorrect response						
True	11	22.4	23	13.4	9	12.5
I don't know	2	4.1	5	2.9	1	1.4
6d: 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	42	85.7 (72.8, 94.1)	147	85.5 (79.3, 90.4)	56	77.8 (66.4, 86.7)
Incorrect response						
False	7	14.3	20	11.6	15	20.8
I don't know	0	0.0	5	2.9	1	1.4

TABLE 6.2.3 SECONDARY 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**

Demonstrated Understanding	S-3a <10 min N=49		S-3b 10 to <20 min N=172		S-3c >= 20 min N=72	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	1	1.4
1 correct response	1	2.0	4	2.3	4	5.6
2 correct responses	5	10.2	15	8.7	5	6.9
3 correct responses	16	32.7	35	20.3	16	22.2
4 correct responses	27	55.1	118	68.6	46	63.9
Average number of correct responses	3.4	(3.0, 4.0)	3.6	(3.3, 4.0)	3.4	(3.1, 4.0)

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=49		S-3b 10 to <20 min N=172		S-3c >= 20 min N=72	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 8: 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.						
8a: Acute or postoperative pain						
Correct response						
No	43	87.8 (75.2, 95.4)	148	86.0 (80.0, 90.9)	62	86.1 (75.9, 93.1)
Incorrect response						
Yes	4	8.2	23	13.4	10	13.9
I don't know	2	4.1	1	0.6	0	0.0

Question	S-3a <10 min N=49		S-3b 10 to <20 min N=172		S-3c >= 20 min N=72	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
8b: Headache or migraine pain						
Correct response						
No	46	93.9 (83.1, 98.7)	148	86.0 (80.0, 90.9)	61	84.7 (74.3, 92.1)
Incorrect response						
Yes	2	4.1	24	14.0	11	15.3
I don't know	1	2.0	0	0.0	0	0.0
8c: Dental pain						
Correct response						
No	46	93.9 (83.1, 98.7)	167	97.1 (93.3, 99.0)	68	94.4 (86.4, 98.5)
Incorrect response						
Yes	0	0.0	4	2.3	3	4.2
I don't know	3	6.1	1	0.6	1	1.4
8d: Breakthrough pain from cancer						
Correct response						
Yes	48	98.0 (89.1, 99.9)	165	95.9 (91.8, 98.3)	67	93.1 (84.5, 97.7)
Incorrect response						
No	1	2.0	7	4.1	5	6.9
I don't know	0	0.0	0	0.0	0	0.0

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=49		S-3b 10 to <20 min N=172		S-3c >= 20 min N=72	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	1	2.0	3	1.7	3	4.2
2 correct responses	1	2.0	8	4.7	6	8.3
3 correct responses	8	16.3	35	20.3	9	12.5
4 correct responses	39	79.6	126	73.3	54	75.0
Average number of correct responses	3.7	(3.3, 4.0)	3.7	(3.4, 4.0)	3.6	(3.2, 4.0)

TABLE 8.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

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=49		S-3b - 10 to <20 min N=172		S-3c - >= 20 min N=72	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.						
6e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.						
Correct response						
True	49	100.0 (92.7, 100.0)	171	99.4 (96.8, 100.0)	72	100.0 (95.0, 100.0)
Incorrect response						
False	0	0.0	1	0.6	0	0.0
I don't know	0	0.0	0	0.0	0	0.0
Question 7: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.						
7a: A personal history of psychiatric illness						
Correct response						
Yes	46	93.9 (83.1, 98.7)	136	79.1 (72.2, 84.9)	60	83.3 (72.7, 91.1)
Incorrect response						
No	3	6.1	23	13.4	9	12.5
I don't know	0	0.0	13	7.6	3	4.2

Question	S-3a - <10 min N=49		S-3b - 10 to <20 min N=172		S-3c - >= 20 min N=72	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
7b: 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	49	100.0 (92.7, 100.0)	171	99.4 (96.8, 100.0)	72	100.0 (95.0, 100.0)
Incorrect response						
No	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	1	0.6	0	0.0
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.						
9a: TIRF medicines can be abused in a manner similar to other opioid agonists.						
Correct response						
True	46	93.9 (83.1, 98.7)	170	98.8 (95.9, 99.9)	70	97.2 (90.3, 99.7)
Incorrect response						
False	3	6.1	1	0.6	2	2.8
I don't know	0	0.0	1	0.6	0	0.0

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=49		S-3b - 10 to <20 min N=172		S-3c - >= 20 min N=72	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
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	1	2.0	1	0.6	0	0.0
3 correct responses	4	8.2	38	22.1	14	19.4
4 correct responses	44	89.8	133	77.3	58	80.6
Average number of correct responses	3.9	(3.4, 4.0)	3.8	(3.5, 4.0)	3.8	(3.4, 4.0)

TABLE 9.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

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=49		S-3b - 10 to <20 min N=172		S-3c - >= 20 min N=72	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.						
9b: TIRF medicines are interchangeable with each other regardless of route of administration.						
Correct response						
False	44	89.8 (77.8, 96.6)	166	96.5 (92.6, 98.7)	70	97.2 (90.3, 99.7)
Incorrect response						
True	4	8.2	3	1.7	2	2.8
I don't know	1	2.0	3	1.7	0	0.0
9c: 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	46	93.9 (83.1, 98.7)	164	95.3 (91.0, 98.0)	67	93.1 (84.5, 97.7)
Incorrect response						
False	1	2.0	3	1.7	1	1.4
I don't know	2	4.1	5	2.9	4	5.6

Question	S-3a - <10 min N=49		S-3b - 10 to <20 min N=172		S-3c - >= 20 min N=72	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.						
Correct response						
True	44	89.8 (77.8, 96.6)	154	89.5 (84.0, 93.7)	68	94.4 (86.4, 98.5)
Incorrect response						
False	2	4.1	6	3.5	2	2.8
I don't know	3	6.1	12	7.0	2	2.8

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=49		S-3b - 10 to <20 min N=172		S-3c - >= 20 min N=72	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	2	4.1	1	0.6	0	0.0
1 correct response	1	2.0	5	2.9	1	1.4
2 correct responses	5	10.2	19	11.0	9	12.5
3 correct responses	41	83.7	147	85.5	62	86.1
Average number of correct responses	2.7	(2.4, 3.0)	2.8	(2.6, 3.0)	2.9	(2.5, 3.0)

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=293		S-5b Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.				
6a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.				
Correct response				
True	257	87.7 (83.4, 91.2)	7	77.8 (40.0, 97.2)
Incorrect response				
False	33	11.3	2	22.2
I don't know	3	1.0	0	0.0
6b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.				
Correct response				
True	280	95.6 (92.5, 97.6)	9	100.0 (66.4, 100.0)
Incorrect response				
False	4	1.4	0	0.0
I don't know	9	3.1	0	0.0

Question	S-5a Internet N=293		S-5b Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
6c: TIRF medicines may be used to treat opioid non-tolerant patients.				
Correct response				
False	242	82.6 (77.8, 86.8)	7	77.8 (40.0, 97.2)
Incorrect response				
True	43	14.7	2	22.2
I don't know	8	2.7	0	0.0
6d: 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	245	83.6 (78.9, 87.7)	6	66.7 (29.9, 92.5)
Incorrect response				
False	42	14.3	3	33.3
I don't know	6	2.0	0	0.0

TABLE 6.2.5 SECONDARY 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**

Demonstrated Understanding	S-5a Internet N=293		S-5b Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	1	0.3	0	0.0
1 correct response	9	3.1	0	0.0
2 correct responses	25	8.5	2	22.2
3 correct responses	67	22.9	3	33.3
4 correct responses	191	65.2	4	44.4
Average number of correct responses	3.5	(3.3, 4.0)	3.2	(2.2, 4.0)

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=293		S-5b - Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
Question 8: 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.				
8a: Acute or postoperative pain				
Correct response				
No	253	86.3 (81.9, 90.1)	8	88.9 (51.8, 99.7)
Incorrect response				
Yes	37	12.6	1	11.1
I don't know	3	1.0	0	0.0
8b: Headache or migraine pain				
Correct response				
No	255	87.0 (82.6, 90.7)	7	77.8 (40.0, 97.2)
Incorrect response				
Yes	37	12.6	1	11.1
I don't know	1	0.3	1	11.1

Question	S-5a - Internet N=293		S-5b - Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
8c: Dental pain				
Correct response				
No	281	95.9 (93.0, 97.9)	9	100.0 (66.4, 100.0)
Incorrect response				
Yes	7	2.4	0	0.0
I don't know	5	1.7	0	0.0
8d: Breakthrough pain from cancer				
Correct response				
Yes	280	95.6 (92.5, 97.6)	8	88.9 (51.8, 99.7)
Incorrect response				
No	13	4.4	1	11.1
I don't know	0	0.0	0	0.0

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=293		S-5b Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0
1 correct response	7	2.4	0	0.0
2 correct responses	15	5.1	1	11.1
3 correct responses	52	17.7	2	22.2
4 correct responses	219	74.7	6	66.7
Average number of correct responses	3.6	(3.5, 4.0)	3.6	(2.5, 4.0)

Table 8.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

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=293		S-5b Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.				
6e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.				
Correct response				
True	292	99.7 (98.1, 100.0)	9	100.0 (66.4, 100.0)
Incorrect response				
False	1	0.3	0	0.0
I don't know	0	0.0	0	0.0
Question 7: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.				
7a: A personal history of psychiatric illness				
Correct response				
Yes	242	82.6 (77.8, 86.8)	7	77.8 (40.0, 97.2)
Incorrect response				
No	35	11.9	2	22.2
I don't know	16	5.5	0	0.0

Question	S-5a Internet N=293		S-5b Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
7b: 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	292	99.7 (98.1, 100.0)	8	88.9 (51.8, 99.7)
Incorrect response				
No	0	0.0	1	11.1
I don't know	1	0.3	0	0.0
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.				
9a: TIRF medicines can be abused in a manner similar to other opioid agonists.				
Correct response				
True	286	97.6 (95.1, 99.0)	9	100.0 (66.4, 100.0)
Incorrect response				
False	6	2.0	0	0.0
I don't know	1	0.3	0	0.0

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=293		S-5b Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0
2 correct responses	2	0.7	1	11.1
3 correct responses	56	19.1	1	11.1
4 correct responses	235	80.2	7	77.8
Average number of correct responses	3.8	(3.6, 4.0)	3.7	(2.6, 4.0)

TABLE 9.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

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=293		S-5b Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.				
9b: TIRF medicines are interchangeable with each other regardless of route of administration.				
Correct response				
False	280	95.6 (92.5, 97.6)	9	100.0 (66.4, 100.0)
Incorrect response				
True	9	3.1	0	0.0
I don't know	4	1.4	0	0.0
9c: 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	277	94.5 (91.3, 96.8)	9	100.0 (66.4, 100.0)
Incorrect response				
False	5	1.7	0	0.0
I don't know	11	3.8	0	0.0

Question	S-5a Internet N=293		S-5b Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
9d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.				
Correct response				
True	266	90.8 (86.9, 93.8)	7	77.8 (40.0, 97.2)
Incorrect response				
False	10	3.4	2	22.2
I don't know	17	5.8	0	0.0

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=293		S-5b Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
0 correct responses	3	1.0	0	0.0
1 correct response	7	2.4	0	0.0
2 correct responses	33	11.3	2	22.2
3 correct responses	250	85.3	7	77.8
Average number of correct responses	2.8	(2.6, 3.0)	2.8	(1.9, 3.0)

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 (PHYSICIANS, ONLY, QUESTION 30)

- **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=12		S-6b 3 - 5 years N=14		S-6c 6 to 15 years N=72		S-6d More than 15 years N=102	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
6a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.								
Correct response								
True	11	91.7 (61.5, 99.8)	12	85.7 (57.2, 98.2)	59	81.9 (71.1, 90.0)	93	91.2 (83.9, 95.9)
Incorrect response								
False	1	8.3	2	14.3	11	15.3	9	8.8
I don't know	0	0.0	0	0.0	2	2.8	0	0.0

Question	S-6a Less than 3 years N=12		S-6b 3 - 5 years N=14		S-6c 6 to 15 years N=72		S-6d More than 15 years N=102	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
6b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.								
Correct response								
True	11	91.7 (61.5, 99.8)	14	100.0 (76.8, 100.0)	70	97.2 (90.3, 99.7)	98	96.1 (90.3, 98.9)
Incorrect response								
False	1	8.3	0	0.0	0	0.0	1	1.0
I don't know	0	0.0	0	0.0	2	2.8	3	2.9
6c: TIRF medicines may be used to treat opioid non-tolerant patients.								
Correct response								
False	12	100.0 (73.5, 100.0)	13	92.9 (66.1, 99.8)	57	79.2 (68.0, 87.8)	80	78.4 (69.2, 86.0)
Incorrect response								
True	0	0.0	1	7.1	12	16.7	19	18.6
I don't know	0	0.0	0	0.0	3	4.2	3	2.9
6d: 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	10	83.3 (51.6, 97.9)	13	92.9 (66.1, 99.8)	55	76.4 (64.9, 85.6)	83	81.4 (72.4, 88.4)
Incorrect response								
False	2	16.7	1	7.1	12	16.7	18	17.6
I don't know	0	0.0	0	0.0	5	6.9	1	1.0

TABLE 6.2.6 SECONDARY 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 (PHYSICIANS, ONLY, QUESTION 30)

- **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=12		S-6b 3 - 5 years N=14		S-6c 6 to 15 years N=72		S-6d More than 15 years N=102	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	1	1.4	0	0.0
1 correct response	0	0.0	0	0.0	4	5.6	3	2.9
2 correct responses	1	8.3	0	0.0	8	11.1	7	6.9
3 correct responses	2	16.7	4	28.6	15	20.8	31	30.4
4 correct responses	9	75.0	10	71.4	44	61.1	61	59.8
Average number of correct responses	3.7	(2.8, 4.0)	3.7	(2.9, 4.0)	3.3	(3.0, 4.0)	3.5	(3.2, 4.0)

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 (PHYSICIANS, ONLY, QUESTION 30)

- **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=12		S-6b 3 - 5 years N=14		S-6c 6 to 15 years N=72		S-6d More than 15 years N=102	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 8: 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.								
8a: Acute or postoperative pain								
Correct response								
No	10	83.3 (51.6, 97.9)	12	85.7 (57.2, 98.2)	65	90.3 (81.0, 96.0)	88	86.3 (78.0, 92.3)
Incorrect response								
Yes	2	16.7	2	14.3	6	8.3	13	12.7
I don't know	0	0.0	0	0.0	1	1.4	1	1.0

Question	S-6a Less than 3 years N=12		S-6b 3 - 5 years N=14		S-6c 6 to 15 years N=72		S-6d More than 15 years N=102	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
8b: Headache or migraine pain								
Correct response								
No	11	91.7 (61.5, 99.8)	12	85.7 (57.2, 98.2)	62	86.1 (75.9, 93.1)	87	85.3 (76.9, 91.5)
Incorrect response								
Yes	1	8.3	2	14.3	10	13.9	13	12.7
I don't know	0	0.0	0	0.0	0	0.0	2	2.0
8c: Dental pain								
Correct response								
No	11	91.7 (61.5, 99.8)	14	100.0 (76.8, 100.0)	69	95.8 (88.3, 99.1)	99	97.1 (91.6, 99.4)
Incorrect response								
Yes	1	8.3	0	0.0	2	2.8	2	2.0
I don't know	0	0.0	0	0.0	1	1.4	1	1.0
8d: Breakthrough pain from cancer								
Correct response								
Yes	12	100.0 (73.5, 100.0)	13	92.9 (66.1, 99.8)	70	97.2 (90.3, 99.7)	93	91.2 (83.9, 95.9)
Incorrect response								
No	0	0.0	1	7.1	2	2.8	9	8.8
I don't know	0	0.0	0	0.0	0	0.0	0	0.0

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 (PHYSICIANS, ONLY, QUESTION 30)

- **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=12		S-6b 3 - 5 years N=14		S-6c 6 to 15 years N=72		S-6d More than 15 years N=102	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	2	2.8	3	2.9
2 correct responses	1	8.3	1	7.1	3	4.2	4	3.9
3 correct responses	2	16.7	3	21.4	10	13.9	24	23.5
4 correct responses	9	75.0	10	71.4	57	79.2	71	69.6
Average number of correct responses	3.7	(2.8, 4.0)	3.6	(2.8, 4.0)	3.7	(3.3, 4.0)	3.6	(3.3, 4.0)

TABLE 8.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

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 (PHYSICIANS, ONLY, QUESTION 30)

- **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=12		S-6b 3 - 5 years N=14		S-6c 6 to 15 years N=72		S-6d More than 15 years N=102	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
6e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.								
Correct response								
True	12	100.0 (73.5, 100.0)	14	100.0 (76.8, 100.0)	72	100.0 (95.0, 100.0)	101	99.0 (94.7, 100.0)
Incorrect response								
False	0	0.0	0	0.0	0	0.0	1	1.0
I don't know	0	0.0	0	0.0	0	0.0	0	0.0

Question	S-6a Less than 3 years N=12		S-6b 3 - 5 years N=14		S-6c 6 to 15 years N=72		S-6d More than 15 years N=102	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.								
7a: A personal history of psychiatric illness								
Correct response								
Yes	8	66.7 (34.9, 90.1)	13	92.9 (66.1, 99.8)	63	87.5 (77.6, 94.1)	83	81.4 (72.4, 88.4)
Incorrect response								
No	4	33.3	0	0.0	7	9.7	14	13.7
I don't know	0	0.0	1	7.1	2	2.8	5	4.9
7b: 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	12	100.0 (73.5, 100.0)	14	100.0 (76.8, 100.0)	72	100.0 (95.0, 100.0)	102	100.0 (96.4, 100.0)
Incorrect response								
No	0	0.0	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 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
9a: TIRF medicines can be abused in a manner similar to other opioid agonists.								
Correct response								
True	11	91.7 (61.5, 99.8)	14	100.0 (76.8, 100.0)	72	100.0 (95.0, 100.0)	98	96.1 (90.3, 98.9)
Incorrect response								
False	1	8.3	0	0.0	0	0.0	3	2.9
I don't know	0	0.0	0	0.0	0	0.0	1	1.0

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 (PHYSICIANS, ONLY, QUESTION 30)

- **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=12		S-6b 3 - 5 years N=14		S-6c 6 to 15 years N=72		S-6d More than 15 years N=102	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
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	0	0.0	0	0.0
3 correct responses	5	41.7	1	7.1	9	12.5	24	23.5
4 correct responses	7	58.3	13	92.9	63	87.5	78	76.5
Average number of correct responses	3.6	(2.7, 4.0)	3.9	(3.1, 4.0)	3.9	(3.5, 4.0)	3.8	(3.4, 4.0)

TABLE 9.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 6: TIME PRACTICING MEDICINE (PHYSICIANS, ONLY, QUESTION 30)

- **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=12		S-6b 3 - 5 years N=14		S-6c 6 to 15 years N=72		S-6d More than 15 years N=102	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
9b: TIRF medicines are interchangeable with each other regardless of route of administration.								
Correct response								
False	11	91.7 (61.5, 99.8)	14	100.0 (76.8, 100.0)	65	90.3 (81.0, 96.0)	97	95.1 (88.9, 98.4)
Incorrect response								
True	1	8.3	0	0.0	4	5.6	4	3.9
I don't know	0	0.0	0	0.0	3	4.2	1	1.0

Question	S-6a Less than 3 years N=12		S-6b 3 - 5 years N=14		S-6c 6 to 15 years N=72		S-6d More than 15 years N=102	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9c: 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	11	91.7 (61.5, 99.8)	13	92.9 (66.1, 99.8)	68	94.4 (86.4, 98.5)	97	95.1 (88.9, 98.4)
Incorrect response								
False	0	0.0	0	0.0	1	1.4	2	2.0
I don't know	1	8.3	1	7.1	3	4.2	3	2.9
9d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.								
Correct response								
True	11	91.7 (61.5, 99.8)	11	78.6 (49.2, 95.3)	65	90.3 (81.0, 96.0)	94	92.2 (85.1, 96.6)
Incorrect response								
False	0	0.0	0	0.0	5	6.9	4	3.9
I don't know	1	8.3	3	21.4	2	2.8	4	3.9

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 (PHYSICIANS, ONLY, QUESTION 30)

- **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=12		S-6b 3 - 5 years N=14		S-6c 6 to 15 years N=72		S-6d More than 15 years N=102	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	1	8.3	0	0.0	2	2.8	0	0.0
1 correct response	0	0.0	0	0.0	1	1.4	3	2.9
2 correct responses	0	0.0	4	28.6	10	13.9	12	11.8
3 correct responses	11	91.7	10	71.4	59	81.9	87	85.3
Average number of correct responses	2.8	(2.0, 3.0)	2.7	(2.0, 3.0)	2.8	(2.4, 3.0)	2.8	(2.5, 3.0)

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 MONTH PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 26):

- **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=42		S-7b 1 – 2 times N=141		S-7c 3 – 5 times N=71		S-7d More than 5 times N=37	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
6a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.								
Correct response								
True	37	88.1 (74.4, 96.0)	120	85.1 (78.1, 90.5)	62	87.3 (77.3, 94.0)	35	94.6 (81.8, 99.3)
Incorrect response								
False	5	11.9	19	13.5	8	11.3	2	5.4
I don't know	0	0.0	2	1.4	1	1.4	0	0.0

Question	S-7a None N=42		S-7b 1 – 2 times N=141		S-7c 3 – 5 times N=71		S-7d More than 5 times N=37	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
6b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.								
Correct response								
True	42	100.0 (91.6, 100.0)	133	94.3 (89.1, 97.5)	66	93.0 (84.3, 97.7)	37	100.0 (90.5, 100.0)
Incorrect response								
False	0	0.0	3	2.1	1	1.4	0	0.0
I don't know	0	0.0	5	3.5	4	5.6	0	0.0
6c: TIRF medicines may be used to treat opioid non-tolerant patients.								
Correct response								
False	31	73.8 (58.0, 86.1)	118	83.7 (76.5, 89.4)	56	78.9 (67.6, 87.7)	34	91.9 (78.1, 98.3)
Incorrect response								
True	9	21.4	19	13.5	13	18.3	3	8.1
I don't know	2	4.8	4	2.8	2	2.8	0	0.0
6d: 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	37	88.1 (74.4, 96.0)	115	81.6 (74.2, 87.6)	58	81.7 (70.7, 89.9)	31	83.8 (68.0, 93.8)
Incorrect response								
False	5	11.9	20	14.2	13	18.3	6	16.2
I don't know	0	0.0	6	4.3	0	0.0	0	0.0

TABLE 6.2.7 SECONDARY 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 MONTH PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 26):

- **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=42		S-7b 1 – 2 times N=141		S-7c 3 – 5 times N=71		S-7d More than 5 times N=37	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	1	0.7	0	0.0	0	0.0
1 correct response	2	4.8	3	2.1	3	4.2	0	0.0
2 correct responses	3	7.1	15	10.6	8	11.3	1	2.7
3 correct responses	9	21.4	35	24.8	17	23.9	9	24.3
4 correct responses	28	66.7	87	61.7	43	60.6	27	73.0
Average number of correct responses	3.5	(3.0, 4.0)	3.4	(3.2, 4.0)	3.4	(3.0, 4.0)	3.7	(3.2, 4.0)

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 MONTH PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 26):

- **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=42		S-7b 1 – 2 times N=141		S-7c 3 – 5 times N=71		S-7d More than 5 times N=37	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 8: 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.								
8a: Acute or postoperative pain								
Correct response								
No	34	81.0 (65.9, 91.4)	122	86.5 (79.8, 91.7)	62	87.3 (77.3, 94.0)	33	89.2 (74.6, 97.0)
Incorrect response								
Yes	7	16.7	17	12.1	9	12.7	4	10.8
I don't know	1	2.4	2	1.4	0	0.0	0	0.0

Question	S-7a None N=42		S-7b 1 – 2 times N=141		S-7c 3 – 5 times N=71		S-7d More than 5 times N=37	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
8b: Headache or migraine pain								
Correct response								
No	38	90.5 (77.4, 97.3)	122	86.5 (79.8, 91.7)	60	84.5 (74.0, 92.0)	31	83.8 (68.0, 93.8)
Incorrect response								
Yes	3	7.1	19	13.5	10	14.1	6	16.2
I don't know	1	2.4	0	0.0	1	1.4	0	0.0
8c: Dental pain								
Correct response								
No	40	95.2 (83.8, 99.4)	136	96.5 (91.9, 98.8)	68	95.8 (88.1, 99.1)	35	94.6 (81.8, 99.3)
Incorrect response								
Yes	1	2.4	3	2.1	1	1.4	2	5.4
I don't know	1	2.4	2	1.4	2	2.8	0	0.0
8d: Breakthrough pain from cancer								
Correct response								
Yes	41	97.6 (87.4, 99.9)	133	94.3 (89.1, 97.5)	66	93.0 (84.3, 97.7)	37	100.0 (90.5, 100.0)
Incorrect response								
No	1	2.4	8	5.7	5	7.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0	0	0.0

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 MONTH PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 26):

- **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=42		S-7b 1 – 2 times N=141		S-7c 3 – 5 times N=71		S-7d More than 5 times N=37	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	2	4.8	2	1.4	1	1.4	2	5.4
2 correct responses	2	4.8	10	7.1	4	5.6	0	0.0
3 correct responses	5	11.9	25	17.7	17	23.9	6	16.2
4 correct responses	33	78.6	104	73.8	49	69.0	29	78.4
Average number of correct responses	3.6	(3.2, 4.0)	3.6	(3.4, 4.0)	3.6	(3.2, 4.0)	3.7	(3.2, 4.0)

Table 8.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

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 MONTH PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 26):

- **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=42		S-7b 1 – 2 times N=141		S-7c 3 – 5 times N=71		S-7d More than 5 times N=37	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 6: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
6e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.								
Correct response								
True	42	100.0 (91.6, 100.0)	140	99.3 (96.1, 100.0)	71	100.0 (94.9, 100.0)	37	100.0 (90.5, 100.0)
Incorrect response								
False	0	0.0	1	0.7	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=42		S-7b 1 – 2 times N=141		S-7c 3 – 5 times N=71		S-7d More than 5 times N=37	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.								
7a: A personal history of psychiatric illness								
Correct response								
Yes	32	76.2 (60.5, 87.9)	116	82.3 (74.9, 88.2)	56	78.9 (67.6, 87.7)	36	97.3 (85.8, 99.9)
Incorrect response								
No	9	21.4	14	9.9	13	18.3	1	2.7
I don't know	1	2.4	11	7.8	2	2.8	0	0.0
7b: 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	42	100.0 (91.6, 100.0)	139	98.6 (95.0, 99.8)	71	100.0 (94.9, 100.0)	37	100.0 (90.5, 100.0)
Incorrect response								
No	0	0.0	1	0.7	0	0.0	0	0.0
I don't know	0	0.0	1	0.7	0	0.0	0	0.0
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
9a: TIRF medicines can be abused in a manner similar to other opioid agonists.								
Correct response								
True	41	97.6 (87.4, 99.9)	140	99.3 (96.1, 100.0)	67	94.4 (86.2, 98.4)	37	100.0 (90.5, 100.0)
Incorrect response								
False	0	0.0	1	0.7	4	5.6	0	0.0
I don't know	1	2.4	0	0.0	0	0.0	0	0.0

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 MONTH PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 26):

- **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=42		S-7b 1 – 2 times N=141		S-7c 3 – 5 times N=71		S-7d More than 5 times N=37	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
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	2	1.4	1	1.4	0	0.0
3 correct responses	11	26.2	25	17.7	17	23.9	1	2.7
4 correct responses	31	73.8	114	80.9	53	74.6	36	97.3
Average number of correct responses	3.7	(3.2, 4.0)	3.8	(3.5, 4.0)	3.7	(3.4, 4.0)	4.0	(3.4, 4.0)

TABLE 9.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 7: NUMBER OF TIMES PER MONTH PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 26):

- **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=42		S-7b 1 – 2 times N=141		S-7c 3 – 5 times N=71		S-7d More than 5 times N=37	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.								
9b: TIRF medicines are interchangeable with each other regardless of route of administration.								
Correct response								
False	40	95.2 (83.8, 99.4)	138	97.9 (93.9, 99.6)	69	97.2 (90.2, 99.7)	33	89.2 (74.6, 97.0)
Incorrect response								
True	2	4.8	0	0.0	2	2.8	3	8.1
I don't know	0	0.0	3	2.1	0	0.0	1	2.7

Question	S-7a None N=42		S-7b 1 – 2 times N=141		S-7c 3 – 5 times N=71		S-7d More than 5 times N=37	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9c: 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	41	97.6 (87.4, 99.9)	131	92.9 (87.3, 96.5)	67	94.4 (86.2, 98.4)	37	100.0 (90.5, 100.0)
Incorrect response								
False	0	0.0	2	1.4	3	4.2	0	0.0
I don't know	1	2.4	8	5.7	1	1.4	0	0.0
9d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.								
Correct response								
True	38	90.5 (77.4, 97.3)	126	89.4 (83.1, 93.9)	65	91.5 (82.5, 96.8)	35	94.6 (81.8, 99.3)
Incorrect response								
False	1	2.4	5	3.5	4	5.6	1	2.7
I don't know	3	7.1	10	7.1	2	2.8	1	2.7

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 MONTH PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 26):

- **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=42		S-7b 1 – 2 times N=141		S-7c 3 – 5 times N=71		S-7d More than 5 times N=37	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
0 correct responses	0	0.0	2	1.4	0	0.0	0	0.0
1 correct response	0	0.0	5	3.5	2	2.8	0	0.0
2 correct responses	7	16.7	12	8.5	8	11.3	6	16.2
3 correct responses	35	83.3	122	86.5	61	85.9	31	83.8
Average number of correct responses	2.8	(2.4, 3.0)	2.8	(2.6, 3.0)	2.8	(2.5, 3.0)	2.8	(2.4, 3.0)