Opioid Postmarketing Requirements Consortium (OPC)

Briefing Document

Anesthetic and Analgesic Drug Products (AADP) and Drug Safety and Risk Management (DSaRM) Advisory Committees

Meeting Date: May 5, 2025

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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2. LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
AADP	Anesthetic and Analgesic Drug Products
ACTTION	Analgesic, Anesthetic, and Addiction Clinical Trials, Translation, Innovations, Opportunities, and Networks
ADF	Abuse-deterrent formulation
ADHD	Attention-deficit/hyperactivity disorder
aHR	Adjusted hazard ratio
aOR	Adjusted odds ratio
BMI	Body mass index
BPD	Borderline personality disorder
BPI-SF	Brief Pain Inventory – Short-Form
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CNS	Central nervous system
CS	Comorbidity score
CYP	Cytochrome P450
DSaRM	Drug Safety and Risk Management
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
GED	General equivalency degree
GEE	General estimating equation
EHR	Electronic health record
ER/LA	Extended-release/long-acting
FDA	Food and Drug Administration
GAD	Generalized anxiety disorder
HCSRN	Health Care Systems Research Network
HR	Hazard ratio
ICD	International Classification of Disease

Abbreviation or Term	Definition
IDS	Integrated delivery system
IQR	Interquartile range
IR/SA	Immediate-release/short-acting
KPNW	Kaiser Permanente Northwest
LtOT	Long-term opioid analgesic therapy
MDD	Major depressive disorder
MME	Morphine milligram equivalents
MOS	Medical Outcome Survey
NDA	New Drug Application
NDI	US National Death Index
NLP	Natural language processing
OOD	Opioid-involved overdose or opioid overdose-related death
OPC	Opioid Postmarketing Requirements Consortium
OPRM1	Opioid receptor mu-1
OR	Odds ratio
OUD	Opioid use disorder
OUD-H	Opioid use disorder involving heroin only
OUD-P	Opioid use disorder involving prescription opioids only
PBRN	Practice-Based Research Network
PCL-5	Post-traumatic stress disorder checklist for DSM-5
PM	Principal molecule
PMR	Postmarketing requirement
POMAQ	Prescription Opioid Misuse and Abuse Questionnaire
PPV	Positive predictive value
PRISM-5-OP	Psychiatric Research Interview for Substance and Mental Disorders, DSM-5 opioid version
PSS	Perceived Stress Scale
PSQI	Pittsburgh Sleep Quality Index

Abbreviation or Term	Definition
PTSD	Post-traumatic stress disorder
py	Person years
Q	Quarter
Rx	Prescription
SD	Standard deviation
SF-12	12-Item Short Form Health Survey
SR-MAD	Self-Reported Misuse, Abuse and Diversion of Prescription Opioids
SUD	Substance use disorder
US	United States
VA	US Department of Veterans Affairs
VUMC	Vanderbilt University Medical Center

A list and description of study-defined terms used in this document is provided in Appendix 9.4.

3. EXECUTIVE SUMMARY

3.1. Introduction

The member companies of the Opioid Postmarketing Requirements Consortium (OPC) have been asked by the United States (US) Food and Drug Administration (FDA) to participate in a joint meeting of the Anesthetic and Analgesic Drug Products (AADP) and Drug Safety and Risk Management (DSaRM) Advisory Committees to discuss the findings of the completed extended-release/long-acting (ER/LA) opioid analgesic postmarketing requirement (PMR) 3033 series of observational studies, with a focus on key studies 3033-1 and 3033-2. These PMR studies are prospective (3033-1) and retrospective (3033-2) epidemiologic studies that examined the serious risks and potential risk factors for misuse, abuse, addiction, and fatal and non-fatal opioid overdose in patients prescribed long-term opioid analgesic therapy for management of chronic pain, including patients prescribed ER/LA opioids.

Chronic pain is a prevalent condition, affecting an estimated 20% of people worldwide (Breivik et al., 2006; Goldberg & McGee, 2011; Gureje et al., 2008; Rikard et al., 2023). Data from the 2023 National Health Interview Survey in the United States (US) found that 24.3% of adults had chronic pain, and 8.5% of adults had chronic pain that frequently limited life or work activities (referred to as high-impact chronic pain) in the prior 3 months (Lucas & Sohi, 2024). Clinical, psychological, and social consequences of chronic pain may limit participation in complex activities, result in lost work productivity, and lead to stigmatization; chronic or persistent pain is among the leading global causes of reduced quality of life (Dahlhamer et al., 2018; Global Burden of Disease Study, 2015).

Patients with chronic pain are treated with a wide range of interventions, with non-steroidal anti-inflammatory drugs and opioid analgesics being among the most common. Opioids have been shown to be efficacious in the treatment of chronic pain for up to 3 – 4 months in randomized controlled trials (e.g., Caldwell et al., 1999; Hale et al., 2007; Jamison et al., 1998; Meske et al., 2018). ER/LA opioids provide an important treatment option for some patients suffering from chronic, persistent pain for which alternative treatment options are inadequate, comprising ~ 11% of opioid analgesic prescriptions in the US in 2022. However, long-term administration of opioids, including ER/LA opioids, may involve risks of serious side effects, such as sedation, respiratory depression, overdose, as well as drug misuse, abuse, or dependence.

3.2. Overview and Objectives of the PMR 3033 Series of Observational Studies

Based on a review of submissions from external interested parties, commenter concerns, and an issue-specific review of literature following a May 2012 National Institutes of Health (NIH) workshop to discuss the efficacy of analgesics for treatment of chronic pain, FDA concluded "*that more data are needed regarding the serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death associated with the long-term use of ER/LA opioid analgesics*." In September 2013, the Agency sent a letter to all companies with approved New Drug Applications (NDAs) for ER/LA opioid analgesics, which outlined the requirement for 5 PMRs (PMR 2065 series of studies), including 4 observational studies and one prospective clinical trial that were to

be conducted as individual companies or as a consortium of companies. In October 2013, OPC was formed to conduct the studies required by the PMRs. The objective of PMR 2065-1, as stated in FDA's letter dated September 10, 2013, was to:

> "***Conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products***"

In February 2016, the 5 original PMRs were expanded to 11 separate studies required to adequately address FDA's study requirements; these PMRs included 10 observational studies and one prospective clinical trial (Table 1). Work on the earliest of these studies was initiated in 2013 following formation of the OPC (refer to Section 3.1 for further details on the study timeframes).

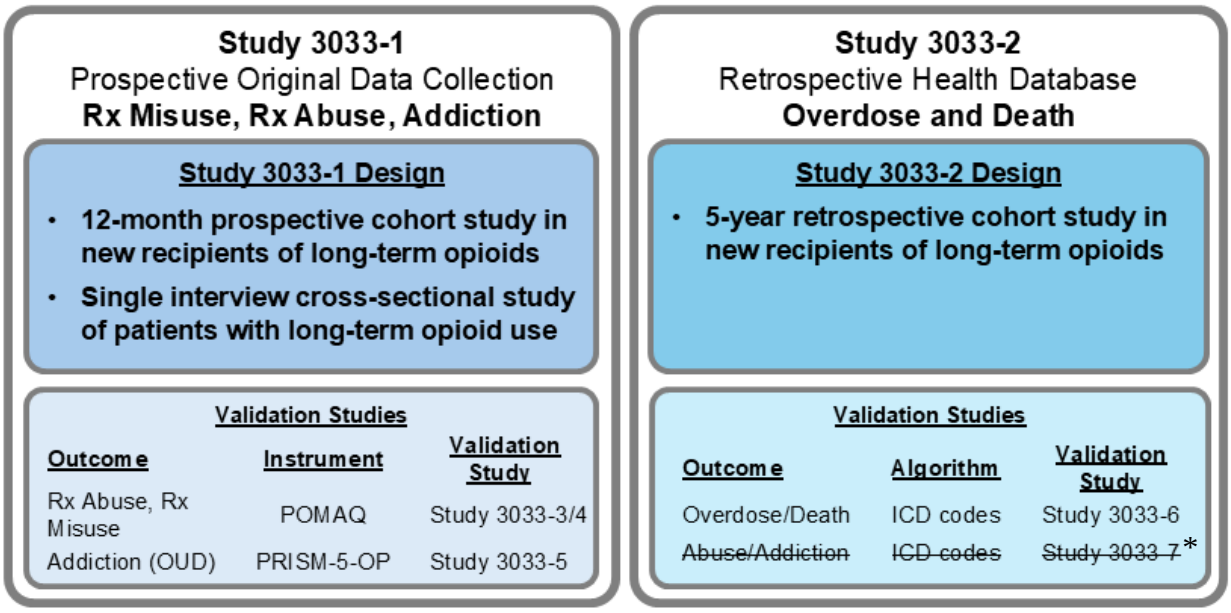
Table 1: Overview of PMR 3033 Studies and Purpose

PMR #	Study Description	Study Purpose
3033-1	Prospective/cross-sectional study of misuse, abuse, and addiction via POMAQ and PRISM-5-OP instruments	Assess incidence and risk factors for misuse, abuse, addiction, overdose, and death among participants prescribed ER/LA opioids
3033-2	Retrospective study of overdose and death in health records, insurance claims, death records	
3033-3	Validation studies of the POMAQ instrument to measure misuse and abuse: Qualitative	Develop and validate measures of misuse, abuse, and addiction
3033-4	Validation studies of the POMAQ instrument to measure misuse and abuse: Quantitative	
3033-5	Validation study of the PRISM-5-OP instrument to measure addiction	
3033-6	Validation of codes to identify opioid-related overdose in databases used in Study 3033-2	Validate coded medical terminologies to identify abuse/addiction, overdose, and death in databases
3033-7	Validation of a diagnostic algorithm to measure abuse/addiction in administrative claims	
3033-8	Cross-sectional study of doctor/pharmacy shopping in a prescription database	Define and validate "doctor/pharmacy shopping" as outcome suggestive of misuse, abuse, and addiction
3033-9	Survey study of doctor/pharmacy shopping in a prescription database vs self-reports	
3033-10	Study of doctor/pharmacy shopping using medical record review	
3033-11	12-Month, randomized, placebo-controlled, double-blind, parallel-group clinical trial in patients with chronic pain	Evaluate the long-term efficacy and safety of an ER/LA opioid in the treatment of chronic pain

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ER/LA = extended-release/long-acting; POMAQ = Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-OP = Psychiatric Research Interview for Substance and Mental Disorders, DSM-5 opioid version.

The primary topic of this Advisory Committee meeting is review of the key observational Studies 3033-1 and 3033-2, along with supporting information from studies (3033-3 to 3033-6) conducted to develop and validate the outcome measures used in the key studies (Figure 1).

Figure 1: Overview of PMR 3033-1 and 3033-2 Observational Studies



ICD = International Classification of Disease; OUD = opioid use disorder; POMAQ = Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-OP = Psychiatric Research Interview for Substance and Mental Disorders, DSM-5 opioid version; Rx = prescription.

Note: Studies 3033-8, 3033-9, and 3033-10 (doctor/pharmacy shopping studies) are not included in the figure, as these are not the primary focus of this briefing document.

* Study 3033-7 was intended to produce algorithms for abuse and addiction using ICD codes. The validation found that the best-performing algorithms lacked sufficient specificity in populations with long-term opioid use to be useful for the study. Therefore, investigators and the OPC, with FDA concurrence, dropped abuse and addiction as an endpoint in Study 3033-2.

3.2.1. Independent Expert and FDA Input on the PMR 3033 Series of Observational Studies

To meet the objectives of the 3033 series of observational studies, OPC engaged independent advisors and investigators from prominent academic and health care institutions to assist with the development, conduct, analysis, and reporting of the studies. The research team included specialists for opioid misuse, abuse and addiction, Clinical Outcomes Assessment experts, and key healthcare providers who manage patients with chronic pain. Input from these external advisors was used to design and conduct both studies, and the protocols and amendments were developed with consensus among these experts.

In addition, FDA reviewed initial draft protocols submitted by OPC, provided written comments, and participated in discussions on the study designs, analysis, and findings. FDA set up the FDA Opioid PMR Steering Committee, which held regular, quarterly meetings to discuss the PMR studies with representatives of the OPC members companies and the study leads. Revisions were implemented in response to FDA feedback, and the study protocols were deemed final by FDA reviewers before the studies could start. The Agency set timelines for completion of the studies and final study reports. As the research evolved and interim results were communicated to FDA, the protocols were modified in accordance with guidance from the Agency; analyses and final

reports were also adjusted in response to FDA Information Requests. For both key studies, the final study results presented herein integrate the protocol-specified analyses and extensions requested by FDA in subsequent Information Requests.

3.3. Overview of Study 3033-1 and Study 3033-2

Both Studies 3033-1 and 3033-2 were observational cohort studies designed to estimate the risks of, and potential risk factors (correlates) associated with the opioid-related study outcomes.

3.3.1. Overview of Study 3033-1 Purpose and Methodology

Study 3033-1 consisted of separate prospective and cross-sectional sub-studies to address the following PMR:

> "*A prospective, observational study designed to quantify the serious risks of misuse, abuse, and addiction associated with long-term use of opioid analgesics for management of chronic pain among patients prescribed ER/LA opioid analgesics. This study must address at a minimum the following specific objectives:*
>
> *a) Estimate the incidence of misuse, abuse, and addiction associated with long-term use of opioid analgesics for chronic pain. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, and addiction.*
>
> b) *Evaluate and quantify other risk factors for misuse, abuse, and addiction associated with long-term use of opioid analgesics for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships*."

Study 3033-1 addressed this PMR using 10 established healthcare systems to estimate the cumulative incidence and prevalence of, and potential risk factors for prescription opioid misuse, prescription opioid abuse, and addiction (assessed as opioid use disorder [OUD]) among patients treated with opioids for chronic pain. Misuse and abuse were assessed using the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), which was validated in Study 3033-3 and Study 3033-4. OUD was evaluated using the Psychiatric Research Interview for Substance and Mental Disorders, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) opioid version (PRISM-5-OP), which was validated in Study 3033-5.

The ***prospective cohort*** sub-study of Study 3033-1 included 1 year of follow-up among a large sample of adults having newly initiated long-term opioid analgesic therapy for chronic pain, to estimate the ***incidence*** of misuse or abuse of prescription opioids, or addiction (assessed as OUD), and to evaluate and quantify risk factors associated with these outcomes. Data collection for the prospective study occurred from August 2017 to October 2021.

The prospective study included 2 subgroups of participants, ER/LA Initiators and Long-Term Opioid Analgesic Therapy Initiators (referred to herein as "LtOT Initiators"). Participants were allocated to one of these cohorts at the time of initial dispensings of opioid analgesics. Patients

were eligible for the *ER/LA Initiators* cohort if they had no ER/LA opioid use within the 6 months prior to their first ER/LA opioid prescription, and then started and refilled a prescription ER/LA opioid (these participants could have used immediate-release/short-acting [IR/SA] opioids within the 6-month period). Although the original intent, as specified in the PMR, was to evaluate patients initiating long-term therapy with ER/LA opioid analgesics, due to changes in clinical practice during the conduct of the study, there were insufficient numbers of patients initiating ER/LA opioid therapy available to meet the sample size requirements within the mandated timeframe. Therefore, a second cohort of participants was added, the *LtOT Initiators* cohort, who were eligible if, after at least 6 months of no ER/LA or Schedule II IR/SA opioid use, they received ER/LA and/or Schedule II IR/SA opioids for at least 70 of 90 days. If a participant qualified for both cohorts at sample selection, priority was given to the ER/LA Initiators cohort. However, it should be noted that the study was not designed, nor intended, to compare the relative risk between different formulations (ER/LA or IR/SA). Rather, with the addition of the LtOT cohort, after conducting the risk factor analyses separately by cohort, the modified protocol specified a comparison of baseline characteristics of the 2 cohorts as a sensitivity analysis. If the 2 cohorts were similar (i.e., distribution of the propensity scores for both cohorts overlapped by $\geq$ 80%) and the findings reasonably convergent, then a sensitivity analysis of incidence and risk factors using a combined cohort was planned to improve study power and precision of estimates. Because the propensity scores did not meet these criteria, the cohorts were analyzed separately.

Detailed objectives and methodologies for the 3033-1 prospective study are provided in Section 5.1.1.

The ***cross-sectional sub-study*** of Study 3033-1 estimated the ***prevalence*** of misuse or abuse of prescription opioids or OUD among a large sample of patients who had used opioid therapy for $\geq$ 1 year. Due to constraints that limited the follow-up period of the prospective study to 1 year, the cross-sectional study was conducted in order to supplement the findings of the prospective study by evaluating patients on long-term opioid analgesic therapy for $\geq$ 1 year. Data for the cross-sectional study were collected from September 2017 to February 2019.

All participants from Study 3033-1, including both the prospective and cross-sectional sub-studies, were recruited from established health systems with comprehensive patient management and claims databases. These settings are varied in geographic location, populations served, care delivery methods, and payment models, and were selected to maximize the applicability of the data to patients using long-term opioid analgesic therapy in routine care.

Detailed objectives and methodologies for the 3033-1 cross-sectional study are provided in Section 5.1.3.1.

In both the prospective and cross-sectional sub-studies, prescription opioid misuse and abuse were assessed using the validated POMAQ questionnaire, and OUD was assessed using the validated PRISM-5-OP instrument. These measures were developed from pre-existing instruments for specific use in the chronic pain population and validated in Studies 3033-3, 3033-4, and 3033-5. A secondary analysis was also performed using different diagnostic definitions and thresholds for evaluating OUD.

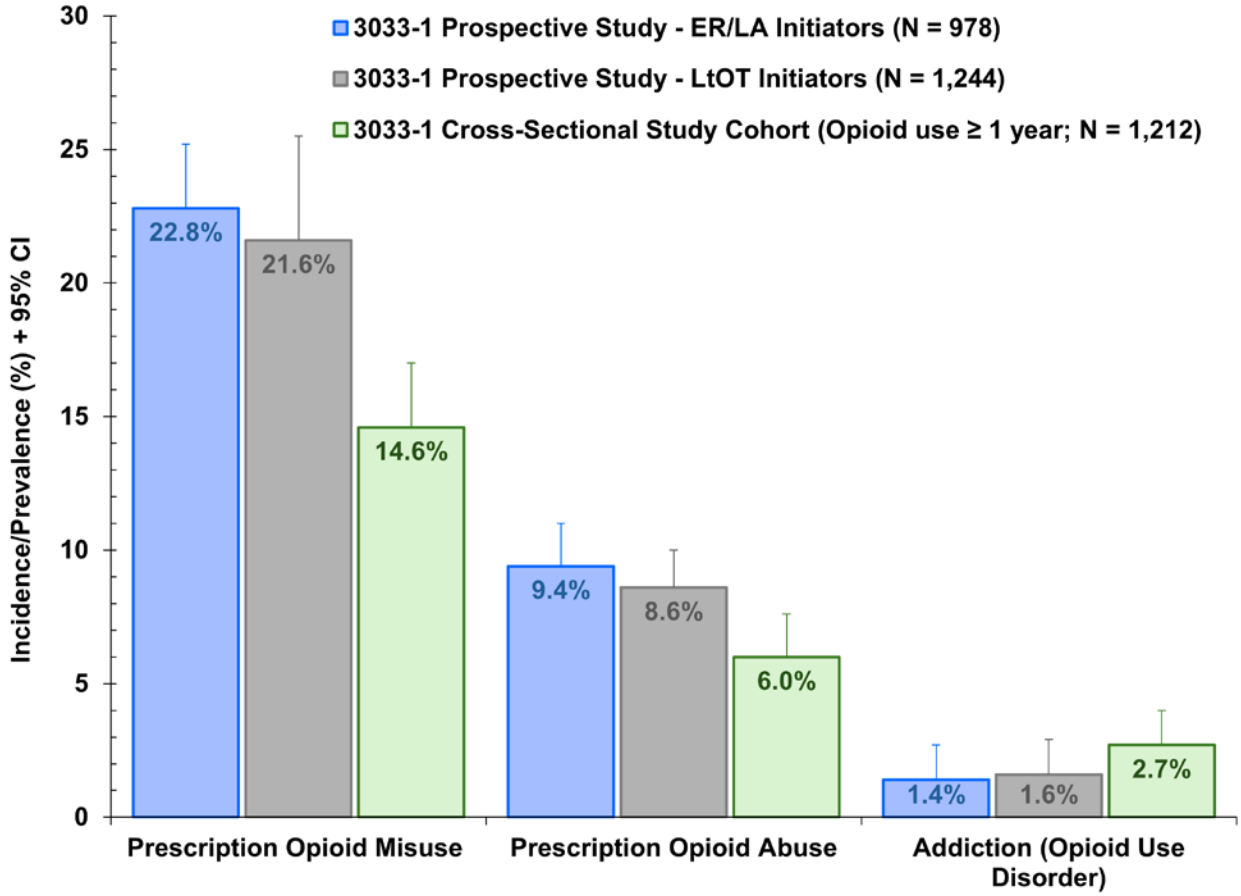
3.3.2. Overview of Study 3033-1 Findings

In both the prospective and cross-sectional studies, participants were generally ≥ 50 years of age, White, and overweight/obese, with multiple comorbidities and dispensing of concomitant medications. Pain diagnoses consisted primarily of back pain and joint/limb/extremity pain. While oxycodone and morphine were the most common opioids used in both the cross-sectional study and the ER/LA Initiators cohort of the prospective study, LtOT Initiators in the prospective study predominantly used hydrocodone, followed by oxycodone. Daily opioid dose (as assessed using milligram morphine equivalents [MMEs] was also higher among cross-sectional study participants (~ 80% using ≥ 50 MMEs per day; 50% ≥ 90 MMEs per day) compared to the ER/LA Opioid Initiators (46% < 50 MMEs per day; 21% ≥ 90 mg/day) and particularly to the LtOT Initiators (86% < 50 MMEs per day; 3% ≥ 90 MMEs per day). Demographics and baseline characteristics of the participants are discussed further in Section 5.1.2.1 (prospective study) and Section 5.1.4.1 (cross-sectional study).

3.3.2.1. Incidence and Prevalence of Prescription Opioid Misuse, Prescription Opioid Abuse, and Addiction (Opioid Use Disorder) – Study 3033-1

In both the prospective and cross-sectional studies (Section 5.1.2.2 and Section 5.1.4.2, respectively), which used the same instruments, adverse opioid-related outcomes occurred with long-term opioid use, and consisted mainly of prescription opioid misuse, with a lower incidence/prevalence of abuse and OUD (Figure 2). The cumulative 12-month incidences of prescription opioid misuse and abuse were similar between ER/LA Initiators (22.8% misuse; 9.4% abuse) and LtOT Initiators (21.6% misuse; 8.6% abuse) in the prospective study (Figure 2). The 12-month cumulative incidences of OUD were also similar between the ER/LA Initiators and LtOT Initiators cohorts (1.4% and 1.6%, respectively), despite differences in use of ER/LA vs. IR/SA opioids and daily MME doses. In the cross-sectional study, prevalences of past-3-month prescription opioid misuse and abuse were 14.6% and 6.0%, respectively, while past-year prevalence of OUD was 2.7% (Figure 2).

Figure 2: Overview of Incidence or Prevalence of Prescription Opioid Misuse, Prescription Opioid Abuse, and Addiction (Opioid Use Disorder) – Study 3033-1



CI = confidence interval; ER/LA = extended-release/long-acting; IR/SA = immediate-release/short-acting; LtOT = long-term opioid analgesic therapy.
ER/LA Initiators: initiation of ER/LA opioid therapy that included ≥ 28 days possession of an ER/LA opioid followed by a subsequent ER/LA prescription, and no ER/LA opioid use in the prior 6 months.
LtOT Initiators: initiation of long-term opioid analgesic therapy, operationalized as ≥ 70 days of opioid possession over a 90-day window with ER/LA and/or Schedule II IR/SA opioids, and no ER/LA or Schedule II IR/SA opioid use in the prior 6 months.
3033-1 Prospective Study Cohorts – 12-month cumulative incidence of prescription opioid misuse, prescription opioid abuse, or OUD (Section 5.1.2.2).
3033-1 Cross-Sectional Study – prevalence of past-3-month prescription opioid misuse or abuse, or past-year opioid use disorder (Section 5.1.4.2).

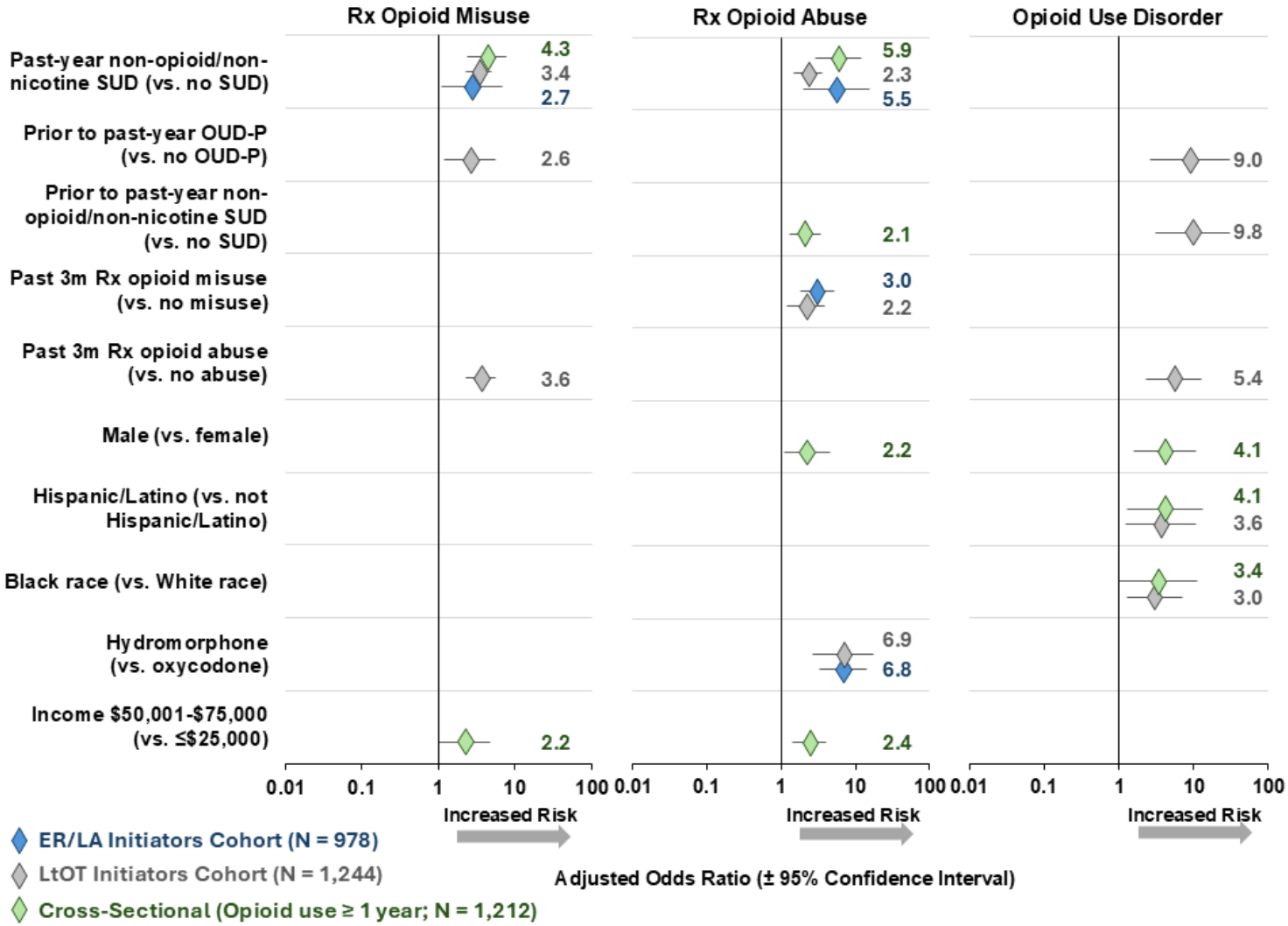
Estimates of OUD varied when using different definitions of OUD and thresholds for diagnosis compared to the primary outcomes. Further information on this analysis is provided in Section 5.1.2.2 (prospective study) and Section 5.1.4.2 (cross-sectional study).

3.3.3. Potential Risk Factors for Prescription Opioid Misuse, Prescription Opioid Abuse, and Addiction (Opioid Use Disorder) – Study 3033-1

Approximately 40 variables, most required by the PMR and previously characterized in the literature, were examined as potential risk factors for the outcomes in Study 3033-1. Because of the large number of variables, those that showed at least double or half the risk of the reference comparator (adjusted odds ratio [aOR] ≥ 2.0 or ≤ 0.5), and which were observed for at least 2 outcomes or in at least 2 cohorts are highlighted here. The factors associated with the strongest increases in risk for misuse, abuse, or OUD across cohorts and outcome measures were primarily related to pre-existing substance use disorders (SUDs) or other pre-existing problematic opioid use behaviors (Figure 3; discussed further in Section 5.1.2.4 and Section 5.1.4.4). Having an annual income $50,000 – $75,000, being male, being Black, or being Hispanic, and predominant use of hydromorphone were associated with increased risks for several outcomes or cohorts. In addition to those shown in Figure 3, use of higher daily opioid doses was an important risk factor for prescription opioid misuse among ER/LA Initiators and for prescription opioid abuse among LtOT Initiators (≥ 120 MMEs or 90 – 119 MMEs, respectively, vs. < 50 MMEs).

Factors associated with the strongest and most consistent decreases in risk (aOR ≤ 0.5) for the primary outcomes are illustrated in Figure 4. Being 50 – 59 years of age (relative to being 18 – 39 years old), being obese, having had exposure to an abuse-deterrent formulation (ADF) and having had more severe comorbidity (as demonstrated by having Elixhauser comorbidity scores of 1 or ≥ 2) were associated with decreased risk for several outcomes or cohorts. In addition to those shown in Figure 4, several other older age categories (e.g., 40 – 49 years or ≥ 60 years) were individually associated with decreased risk for at least one outcome. Additional risk factors were important for individual outcomes or in specific cohorts (as outlined in Section 5.1.2.4 and Section 5.1.4.4). Overall, many of the risk factors identified in Study 3033-1 were broadly consistent with those reported in published studies.

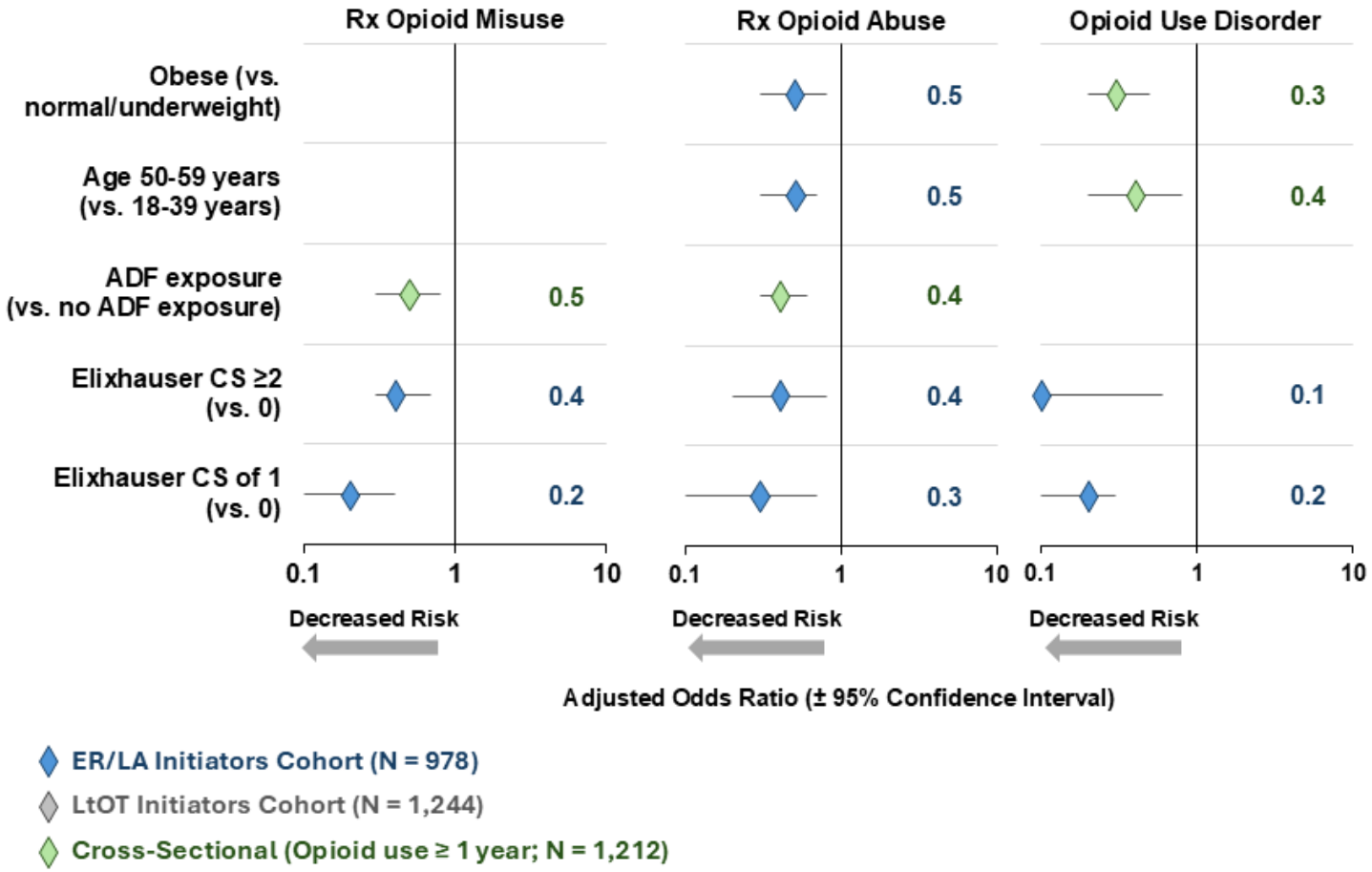
Figure 3: Strongest Potential Risk Factors Associated with Increased Risk (Adjusted Odds Ratio ≥ 2.0) for at Least 2 Outcomes or Cohorts in the Fully-Adjusted Models – Study 3033-1



ER/LA = extended-release/long-acting; LtOT = long-term opioid analgesic therapy; m = month; OUD-P = opioid use disorder involving prescription opioids; Rx = prescription; SUD = substance use disorder.

Note: Includes risk factors observed in ≥ 2 outcomes or ≥ 2 cohorts (operating in the same direction) from fully-adjusted models (only cohorts meeting criteria are shown). Important risk factors (aOR ≥ 2.0) in only one cohort/outcome are summarized in Sections 5.1.2.4 (Prospective) and 5.1.4.4 (Cross-Sectional). All statistically significant risk factors are shown in Appendix 9.1.1.3 (Prospective) and 9.1.2.1 (Cross-Sectional).

Figure 4: Strongest Potential Risk Factors Associated with Decreased Risk (Adjusted Odds Ratio ≤ 0.5) for at Least 2 Outcomes or Cohorts in the Fully-Adjusted Models – Study 3033-1



ADF = abuse-deterrent opioid; CS = comorbidity score; Rx = prescription; ER/LA = extended-release/long-acting; LtOT = long-term opioid analgesic therapy.
Note: Includes risk factors observed in ≥ 2 outcomes or ≥ 2 cohorts (operating in the same direction) from fully-adjusted models (only cohorts meeting criteria are shown). Important risk factors (aOR ≤ 0.5) in only 1 cohort/outcome are summarized in Sections 5.1.2.4 (Prospective) and 5.1.4.4 (Cross-Sectional). All statistically significant risk factors are shown in Sections 9.1.1.3 (Prospective) and Section 9.1.2.1 (Cross-Sectional).

3.3.4. Overview of Study 3033-2 Purpose and Methodology

Study 3033-2 was a retrospective cohort study designed to address the following PMR:

"*An observational study designed to measure the incidence and predictors of opioid overdose and death (OOD, as well as opioid abuse/addiction, using patient health records, insurance claims, and death records. This study must address at a minimum the following specific objectives:*

a) Estimate the incidence of abuse/addiction, overdose, and death associated with long-term use of opioid analgesics for chronic pain. Stratify overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of abuse/addiction, overdose, and death.

b) *Evaluate and quantify other risk factors for abuse/addiction, overdose, and death associated with long-term use of opioid analgesics for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify overdose by intentionality wherever possible*."

Study 3033-2 was a retrospective cohort consisting of a large number of individuals in routine care covered by health insurance. The study reviewed the experience of new long-term users of Schedule II opioids as recorded in 4 administrative healthcare databases. The goal was to quantify the cumulative incidence of opioid-involved overdose or opioid overdose-related death (OOD) over several years. The algorithm used to define OOD was validated against medical records in a variety of settings in Study 3033-6. An effort to define abuse/addiction as a study outcome using insurance claims had proven unsuccessful in companion Study 3033-7. Study 3033-2 further examined factors that might modify the risk of OOD.

Study 3033-2 relied on data from commercial and non-profit insurers, and from one Medicaid program, supplemented by the US National Death Index (NDI) and by medical records for validation. Cohort members were included if they had ≥ 70 days of opioid dispensings in a 90-day "Qualification Period" that immediately preceded the start of follow-up. Potential risk factors were drawn from characteristics of person, place, and exposure identifiable during the Qualification Period. Observation terminated with the occurrence of OOD, exit from the members' insurance plans, aging out, study termination, or the occurrence of one of a small number of disqualifying events. Study 3033-2 covered data accrued from October 2006 to December 2017, with the last cohort entry occurring in December 2016.

Detailed objectives and methodology for Study 3033-2 are provided in Section 5.2.2.

3.3.5. Overview of Study 3033-2 Findings

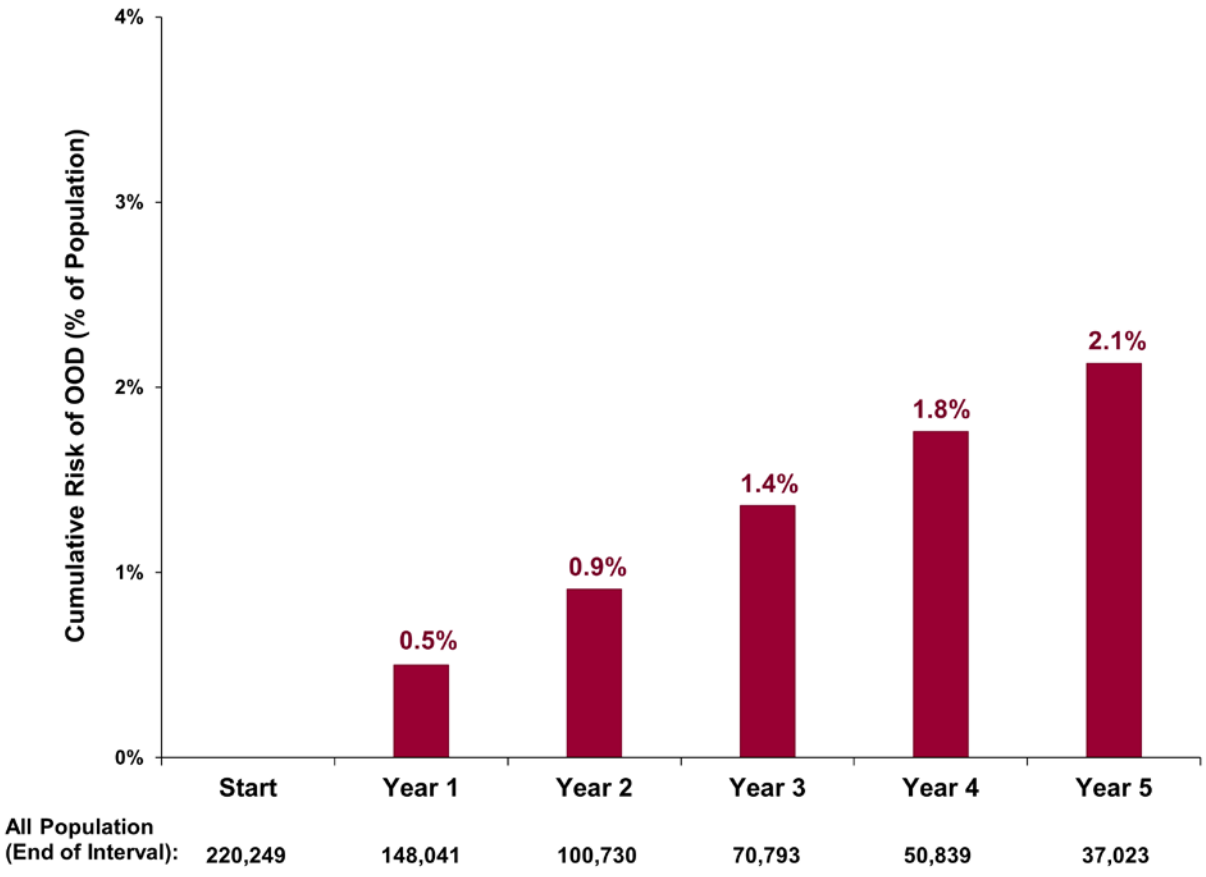
At baseline in Study 3033-2, most cohort members were ≥ 45 years of age, with an approximately even split between males and females. Most of the cohort was resident in the South US Census Region, followed by the West. IR/SA hydrocodone was the most common

principal molecule dispensed at baseline, followed by IR/SA oxycodone. Psychiatric comorbidities and other medication use were relatively common. SUD diagnoses prior to cohort entry were present in ~ 5% of cohort members. Most cohort members continued to receive dispensings of opioids, non-opioid analgesics, muscle relaxants, and other medications throughout the follow-up period. Further information on demographic and baseline characteristics of cohort members are provided in Section 5.2.3.2.1.

3.3.5.1. Risk of Opioid-Involved Overdose or Opioid Overdose-Related Death (OOD) – Study 3033-2

Study 3033-2 found a site-average risk of OOD of 0.50% by the end of the first year of observation, rising to 2.13% at end of the fifth year (Figure 5). There was an average incidence of 5.3 per 1000 person-years across for all sites (Section 5.2.3.1.1).

Figure 5: Cumulative Risk of Opioid-Involved Overdose or Opioid Overdose-Related Death (OOD) Through 5 Years – Study 3033-2



OOD = opioid-involved overdose or opioid overdose-related death.
Overall risk of OOD is described further in Section 5.2.3.1.1.

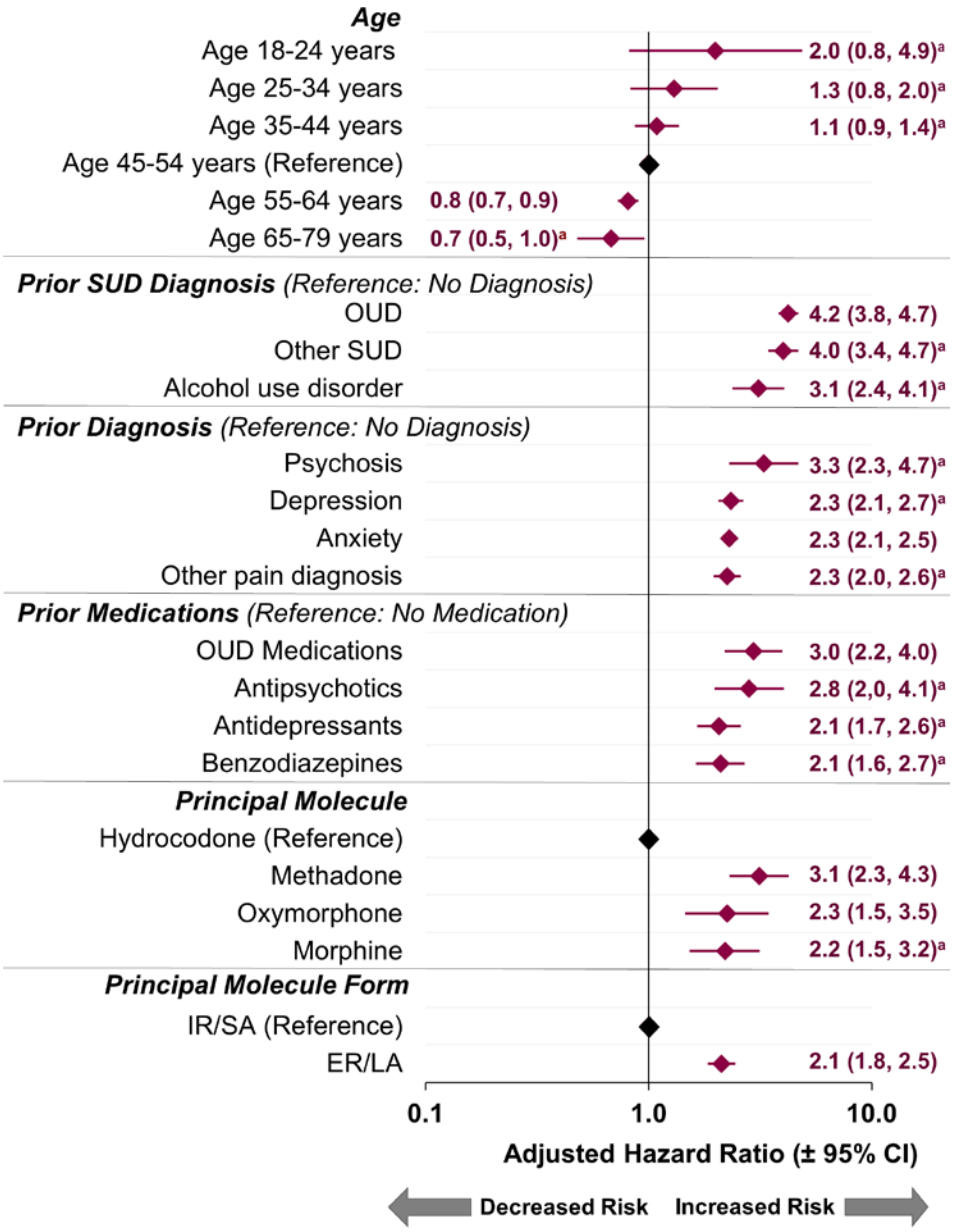
The risk of OOD was highest in the site that used only Medicaid data (Vanderbilt University Medical Center [VUMC]), lower in the sites using national commercial insurance data

(HealthCore and Optum), and lowest in the non-profit health care system (Kaiser Permanente Northwest [KPNW]).

3.3.5.2. Potential Risk Factors for Opioid-Involved Overdose or Opioid Overdose-Related Death (OOD) – Study 3033-2

In Study 3033-2, risk for OOD declined steadily with age, the youngest cohort members (aged 18 – 24 years) having nearly 3 times the risk of the oldest members (65 – 79) (Figure 6). Sex, region and calendar year made only minor further contributions to variation in risk (Section 5.2.3.1.2). In analyses of baseline potential risk factors for later OOD, with adjustment for age, sex, region and calendar era, the strongest determinant of risk was the initial dose of opioid, as measured in MMEs during the Qualification Period (Figure 7). Other baseline factors that were highly predictive of OOD in models adjusted for age, sex, region and calendar era included certain opioids dispensed at baseline (e.g., principal molecules methadone, oxymorphone, and morphine), dispensing of ER/LA opioids (vs. IR/SA opioids), and prior diagnoses of SUDs, and other psychiatric disorders and associated medications (Figure 6). Each of these predictions was attenuated when mutually adjusted, particularly after control for baseline opioid dose (Qualification MMEs), suggesting that these features correlated with one another and with shared underlying risk factors for the outcome of OOD.

Figure 6: Strongest Potential Risk Factors (Adjusted Hazard Ratio ≥ 2.0) for Opioid-Involved Overdose or Opioid Overdose-Related Death (OOD) across all 4 Sites (Adjusted for Age, Sex, Calendar Era and Census Region) – Study 3033-2



CI = confidence interval; ER/LA = extended release/long-acting; IR/SA = immediate-release/short-acting; KPNW = Kaiser Permanente Northwest; MME = morphine milligram equivalents; OOD = opioid-involved overdose or opioid-overdose-related death; OUD = opioid use disorder; SUD = substance use disorder.

[a.] Hazard ratios associated with heterogeneity indices of ≥ 0.50 indicating inter-site variation.

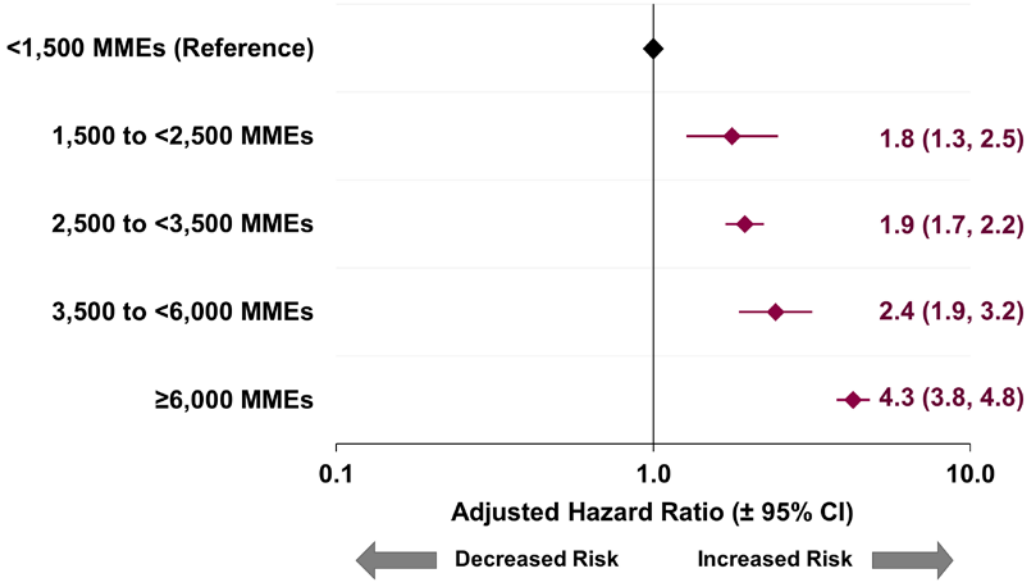
Data for percentage of cohort, heterogeneity index (I^2), number of sites, and p-values are shown in Appendix 9.2.1.

Notes: Medications for OUD were generally not recorded at KPNW because substance use treatment was contracted outside of the KPNW system. The corresponding summary is across the remaining 3 sites.

The principal molecule was the Schedule II opioid chemical entity that contributed the most MMEs to the course of therapy that qualified a person for entry into the cohort. The chemical entity and the form of the principal molecule were tabulated separately.

For prior diagnoses/medications, each term was modeled as present or absent. Absent (not shown) is the reference.

Figure 7: Hazard Ratios for Baseline Opioid Dose (Qualification Period MMEs[a]) as a Potential Risk Factor for Opioid-Involved Overdose or Opioid Overdose-Related Death (OOD) across all 4 Sites (Adjusted for Age, Sex, Calendar Era and Census Region) – Study 3033-2



CI = confidence interval; MMEs = morphine milligram equivalents; OOD = opioid-involved overdose or opioid-overdose-related death.
[a.] Total MMEs of Schedule II opioids dispensed during the 90-day Qualification Period prior to Cohort Start Date. Percentage of cohort, heterogeneity index (I^2), number of sites, and p-values are provided in Appendix 9.2.1.

A variety of sub-studies addressing secondary goals indicated that the findings were robust to prespecified variations in the definitions of new use, restriction to observation during continuous opioid use, restriction to OOD not classified as the result of intentional self-harm, stratification by major risk factors, and introduction of new opioid regimens during the course of follow-up.

A Switch/Add cohort (N = 53,257) evaluated patients who had IR/SA opioid dispensings in the baseline period and subsequently switched to or added on either a different IR/SA opioid (N = 41,685) or an ER/LA opioid (N = 11,572) (Section 5.2.3.2.5). Persons who introduced ER/LA opioids experienced higher rates of OOD than persons who introduced IR/SA opioids (either 4 or 6 added events per 1,000 py, depending on the rule for end of follow-up). Cohort members in the ER/LA Switch/Add group were dispensed higher opioid doses before the introduction of the new opioid than those in the IR/SA Switch/Add group. Further, median daily opioid dose increased by ~ 53% over the 90-day post-index date period after a Switch/Add to an ER/LA opioid, while median daily MME decreased by ~ 41% from before to after a Switch/Add event in the IR/SA Switch/Add group. These findings raise the possibility that the risk may have been attributable in part to the new treatment regimens' inclusion of an increase in dose along with a change in formulation.

3.4. Overview of Study 3033-1 and 3033-2 Strengths and Limitations

Consistent with the PMRs, the 3033 series of observational studies were descriptive in nature, intended to fill knowledge gaps that existed at the time of the PMR issuance, and not to delineate cause and effect.

For Study 3033-1, the timeframe of data collection was during a period when abuse of prescription opioids was already decreasing (i.e., after 2017), due in part to clinical practice guidelines and changes in state and payer policies initiated during or after 2016 (as discussed further in Section 6.3). Strengths of Study 3033-1 prospective and cross-sectional sub-studies included the geographic diversity of sites, with recruitment from the large and complete data systems of different types of healthcare organizations, selected for variability in populations served, insurance coverage, and geographic location.

In Study 3033-2, exposure measures were based on pharmacy dispensings recorded by insurance plans at baseline and do not describe patients' use, which is inferred from the pattern of prescription fills. Treatment was not randomized, so that even after control for measured covariates, residual confounding remains a possibility. The timeframe of the data source (2006 – 2017) included periods that preceded contemporary clinical practice guidelines and state/payer policies, as noted above for Study 3033-2. Strengths of Study 3033-2 were the inclusion of a range of US healthcare settings, large size, consistency and completeness of insurance data, and the opportunity for follow-up over several years.

Both studies employed validated outcome measures and assessed numerous potentially important risk factors for the outcomes.

3.5. Conclusions

Conclusions that can be drawn from Study 3033-1 include:

- Prescription opioid misuse (intentional use for therapeutic purposes outside label directions or other than prescribed or directed by prescriber), was common among patients with long-term use of opioid analgesics for the treatment of chronic pain.
- The rate of new onset moderate-to-severe OUD among patients with chronic pain prescribed opioids long-term was estimated to be ~ 2% when using the pain-adjusted measure employing DSM-5 criteria that was developed for this study (may be referred to elsewhere as "PRISM-5-OP OUD").
- Study 3033-1 (cross-sectional sub-study) found a past-year prevalence of moderate-to-severe OUD of 2.7% using the pain-adjusted measure.
- The factors associated with the strongest and most consistent increases in risk for prescription opioid misuse or abuse, or OUD were pre-existing SUDs or other pre-existing problematic opioid use behaviors.

Conclusions that can be drawn from Study 3033-2 include:

- Initiation of long-term opioid use marked the onset of a multi-year period of continued use of opioids (~ 80% of the cohort) and other medications usually considered to put patients at risk for complications of opioid therapy.
- There was a continued occurrence of OOD for at least 5 years after opioid initiation (0.5% per year in the 4 study sites).
- Higher baseline dose of opioids was strongly associated with higher subsequent risk of OOD.
- Prior diagnoses of mental health disorders, particularly SUDs, and medications used to treat these disorders, were associated with elevated risk of OOD.
- Use of ER/LA opioids was strongly associated with high-dose opioid regimens, posing a challenge to efforts to disentangle the effects of formulation and dose.

The observational studies were suited to the purpose of the PMRs and the studies addressed evidence gaps related to long-term opioid analgesic use. Validated research measures for misuse, abuse, and addiction were developed and the validity of an existing database algorithm for OOD was confirmed. The incidence of the 5 outcomes related to long-term opioid use in patients with chronic pain was quantified and many prespecified demographics/characteristics were evaluated and the strongest potential risk factors for the outcomes were identified. The risks and risk factors identified in Studies 3033-1 and 3033-2 were broadly consistent with those previously reported in the scientific literature. The studies added a coordinated, validated, large-scale set of findings.

4. INTRODUCTION

The member companies of the OPC have been asked by the US FDA to participate in a joint meeting of the AADP and DSaRM Advisory Committees. The purpose of the Advisory Committee meeting is to discuss the findings of the completed ER/LA opioid analgesic observational study PMRs, the prospective Study 3033-1 and the retrospective Study 3033-2, which examined the serious risks of and risk factors for misuse, abuse, addiction, and fatal and non-fatal opioid overdose, in patients with long-term use of opioid analgesics for management of chronic pain, including patients prescribed ER/LA opioid analgesics.

4.1. Formation of the OPC and Overview of the 3033 Series of Observational Studies

In May 2012, FDA held a public scientific workshop at NIH to discuss efficacy of analgesics in chronic non-cancer pain. Concerns were raised at the workshop about the safety of opioids at higher doses, including risks for misuse, abuse, addiction, overdose, and death. Following a review of participant comments, submissions from external interested parties, and an issue-specific review of scientific literature, FDA concluded more data were needed. In September 2013, the Agency sent a letter to all companies with approved NDAs for ER/LA opioid analgesics, which outlined the requirement for 5 PMRs (4 observational studies and one prospective clinical trial) to be conducted as individual companies or as a consortium of companies.

In October 2013, OPC was formed to conduct the studies required by the PMRs. OPC initially included 9 member companies (Allergan, Inc., Endo Pharmaceuticals, Inc., Hikma Pharmaceuticals, P.L.C., Janssen Pharmaceuticals, Inc., Mallinckrodt Pharmaceuticals, P.L.C., Pfizer Inc, Purdue Pharma L.P., Zogenix Inc., and Rhodes Pharmaceuticals L.P.), eventually, by the end of 2018, increasing its membership to 13 companies, as FDA approved new ER/LA opioid analgesic products (the following companies were added, while a few of the original companies departed: Persion Pharmaceuticals, L.L.C., Assertio Therapeutics, Inc., Collegium Pharmaceutical, Inc., BioDelivery Sciences International, Inc., Daiichi Sankyo Limited, and Egalet Corporation). As companies have discontinued or divested their ER/LA opioid products, the number of member companies has steadily decreased. Currently, OPC comprises 3 member companies (Collegium Pharmaceutical, Inc., Endo USA, Inc., and Purdue Pharma L.P).

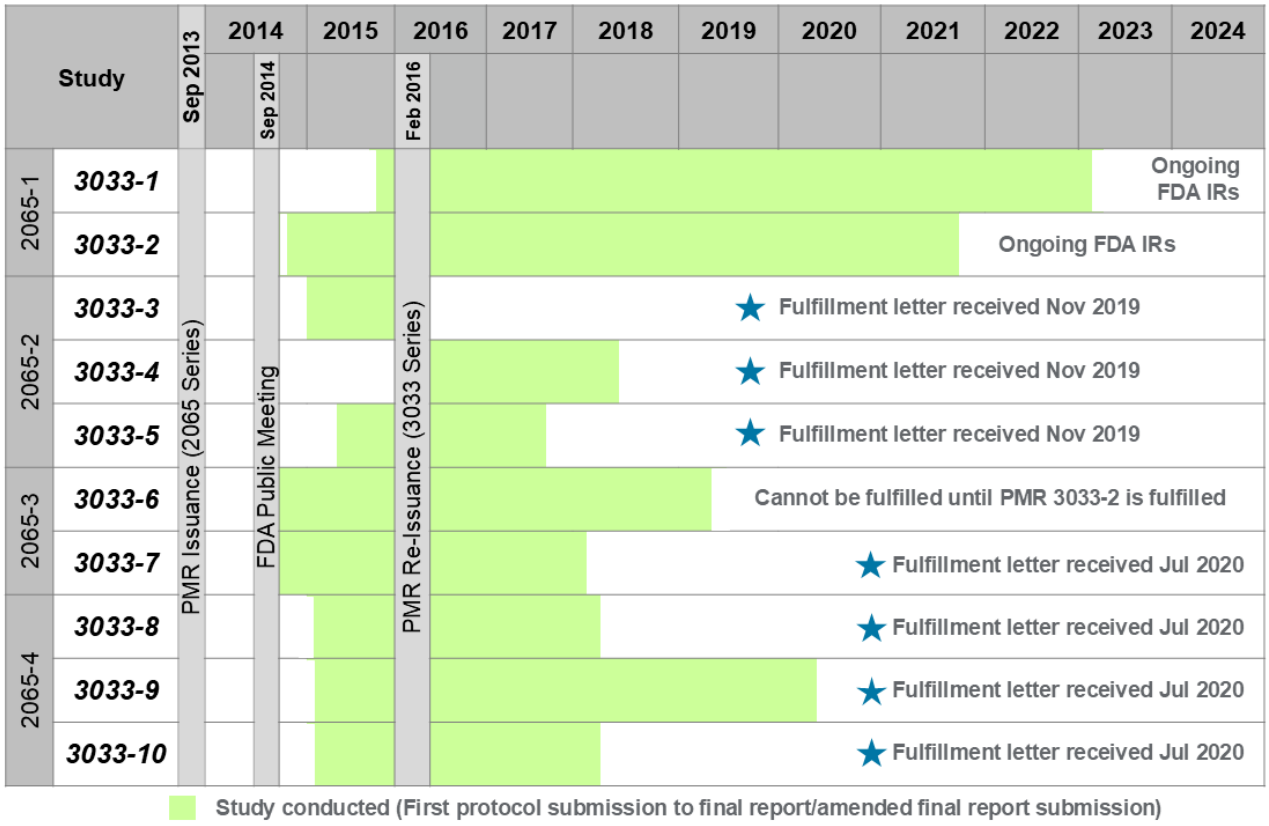
As outlined in Figure 8, development of these studies began following the September 2013 issuance of a set of ER/LA opioid PMRs (2065 series) and formation of the OPC. In May 2014, FDA held an open public meeting with a panel of more than 30 relevant experts selected by FDA to review the study proposals developed by OPC. Draft study protocols were presented during the meeting, and feedback from the experts was incorporated into the protocols. In addition to the 2014 public meeting, between 2013 and 2016, there were a number of activities related to addressing the PMRs outlined in the 2013 letter, including ongoing discussions between OPC and FDA on methodology and study design. In February 2016, the 5 original PMRs were expanded to 11 separate studies to adequately address FDA's study requirements. The 11 PMRs included 10 observational studies and one prospective clinical trial. The mapping of the original 2065 series to the 3033 series of PMRs is outlined in Figure 8 below.

To date, OPC has completed all 10 observational studies; 7 studies have been determined by FDA to fulfill the PMR requirements, while 3 studies have been submitted and are under FDA review for PMR fulfillment. The validation studies for outcome measures used in Studies 3033-1 (3033-3, 3033-4, and 3033-5) and 3033-2 (3033-6) were completed, and final reports were submitted in 2018. Fulfillment letters for 3 of these studies (3033-3, 3033-4, and 3033-5) were received in November 2019 (Study 3033-6 cannot be deemed fulfilled until fulfillment of Study 3033-2). Fulfillment letters for validation Study 3033-7 and 3 doctor/pharmacy shopping studies (3033-8, 3033-9, and 3033-10) were received in July 2020. Study 3033-7 is summarized in Appendix 9.3.2.2; further information can be found in Carrell et al., 2020 and FDA's evaluation of the study (https://www.fda.gov/media/141356/download?attachment). A discussion of Studies 3033-8, 3033-9, and 3033-10 (the doctor/pharmacy shopping studies) is beyond the scope of this briefing document. Detailed information on the methods and findings have been published, including FDA's evaluations of these studies:

- Study 3033-8: Walker et al., 2017; Walker et al., 2019; FDA evaluation at https://www.fda.gov/media/141357/download?attachment
- Study 3033-9: Stephenson et al., 2020; FDA evaluation at https://www.fda.gov/media/141358/download?attachment
- Study 3033-10: Esposito et al., 2019, FDA evaluation at https://www.fda.gov/media/141348/download?attachment.

The prospective and cross-sectional sub-studies of Study 3033-1 collected data from August 2017 to October 2021, and from September 2017 to February 2019, respectively. The retrospective Study 3033-2 covered data accrued from October 2006 to December 2017, with the last cohort entry occurring in December 2016. Studies 3033-1 and 3033-2 have been completed, with the amended final reports submitted to FDA in the first quarter (Q1) of 2023 and third quarter (Q3) of 2021, respectively. Extensions to the analyses for both studies have continued following receipt of subsequent FDA Information Requests. Findings from Studies 3033-1 and 3033-2 will be submitted to peer-reviewed journals for publication once it is confirmed that no additional analyses are needed.

Figure 8: Timeline of Development and Completion of PMR 3033 Series of Observational Studies



FDA = Food and Drug Administration; IR = Information Request; PMR = postmarketing requirement.

Throughout the investigational process, OPC engaged a scientific advisory board, including a series of independent advisors and investigators from prominent academic and health care institutions with expertise in observational studies to assist with the development, conduct, analysis, and reporting of the PMR 3033 series of observational studies.

FDA reviewed draft protocols submitted by OPC, provided written comments, and participated in discussions on the study designs, analytical plans, and generalizability of findings, including quarterly meetings of the FDA Opioid PMR Steering Committee with representatives from OPC member companies. The revised study protocols were deemed final by FDA reviewers before the studies could start, and the Agency set timelines for completion of the studies and final study reports (Coplan et al., 2020). The protocols represented agreed-upon implementations of the PMRs that elaborated on the original PMR language in a higher specificity of research goals, and with accommodations for the infeasibility of obtaining some data items in large populations. As the research evolved and interim results were communicated to FDA, the protocols were modified in accordance with guidance from the Agency. Analyses and final reports were also adjusted in response to FDA Information Requests. For example, in the case of Study 3033-2, FDA issued a consequential Information Request about dose quantification as the draft Final Report was being prepared in accordance with the agreed deadline. Further requests followed, addressing dose adjustment and dose measures in the “Switch/Add” sub-study (described in

Section 5.2.3.2.5 below). Since analyses conducted in response to FDA Information Requests provide valuable information for the interpretation of the findings, for both the 3033-1 and 3033-2 studies, the final results presented herein integrate the protocol-specified analyses and the extensions to analyses due to subsequent FDA Information Requests.

5. SUMMARY OF 3033-1 AND 3033-2 OBSERVATIONAL STUDIES

5.1. Study 3033-1: A Prospective Investigation of the Risks of Opioid Misuse, Abuse, and Addiction Among Patients Treated with Opioids for the Treatment of Chronic Pain

Study 3033-1 consisted of 2 sub-studies:

1) A prospective cohort study with 1 year of follow-up among patients with newly initiated long-term opioid use to estimate the ***incidence*** of misuse or abuse of prescription opioids or addiction (as measured by OUD), and to evaluate and quantify potential risk factors associated with these adverse outcomes; and

2) A cross-sectional study among patients who had used opioid therapy for at least 1 year to estimate the ***prevalence*** of misuse or abuse of prescription opioids or OUD, and to evaluate and quantify potential risk factors associated with these adverse outcomes.

PMR 3033-1 required descriptive estimates of the outcomes and potential risk factors; therefore, no causal relationships were assessed in the studies. However, observations regarding potential risk factors were refined through additional multivariate analyses.

5.1.1. Study 3033-1 – Prospective Study Objectives and Methodology

5.1.1.1. 3033-1 Prospective Study – Objectives and Outcomes

The primary objective of the prospective, observational study was to quantify the *incidence* of and potential risk factors for misuse of prescription opioids, abuse of prescription opioids, and/or OUD among patients on long-term opioid analgesic therapy by:

1. Estimating the 12-month cumulative incidence of ***misuse*** of prescription opioids, ***abuse*** of prescription opioids, and ***OUD*** (primary outcomes), and a composite of any of these outcomes (secondary outcome).

The working definitions of misuse and abuse for this study were modified versions of definitions obtained from the Analgesic, Anesthetic, and Addiction Clinical Trials, Translation, Innovations, Opportunities, and Networks (ACTTION) review (Smith et al., 2013) and are as follows:

> ***Misuse*** was defined as the intentional use of a drug for therapeutic purpose (to reduce an aversive symptom or state) in a manner that is inappropriately outside label directions, or in a manner other than prescribed or directed by an HCP. This definition included patients using a drug for a condition different from that for which the drug was prescribed,

patients taking more drugs than prescribed, or patients using a drug at different dosing intervals.

Abuse was defined as the intentional use of a drug for non-therapeutic purposes, repeatedly or sporadically, for the purpose of achieving a positive psychological or physical effect.

Prescription opioid misuse and abuse were determined using the POMAQ (the Prescription Misuse and Abuse Questionnaire). The POMAQ was developed because there was no existing instrument that had been validated for assessing misuse and abuse in patients using opioid analgesics for chronic pain. The POMAQ was based on a previous instrument, the Self-Reported Misuse, Abuse and Diversion of Prescription Opioids (SR-MAD) that was initially developed to assess opioid misuse, abuse and diversion, with an emphasis on tampering with opioid pain medications (Setnik et al., 2015; Setnik et al., 2017). The SR-MAD was substantially modified following input from OPC's Observational Study Working Group members and FDA-invited expert review to revise questions and to include additional questions regarding misuse and abuse behaviors to meet the objectives of the PMR study. **Study 3033-3** was a qualitative, cognitive interview study among patients with chronic pain to ensure that the content and questions of the POMAQ were understood by patients and relevant to their experiences (Coyne et al., 2021a; Coyne et al., 2023; Appendix 9.3.1.1). **Study 3033-4** was a cross-sectional validation study that confirmed the validity and reproducibility of the POMAQ to identify opioid abuse and misuse behaviors among participants with chronic pain requiring long-term opioid use (Coyne et al., 2021b; Coyne et al., 2021c; Appendix 9.3.1.2). The clinical scoring algorithm of the POMAQ (Appendix 9.1.1.1) underwent a rigorous clinical validation (Coyne et al., 2022) to ensure that it reflected clinically relevant patient behaviors and thresholds. Note that occurrence of ≥ 1 misuse or abuse behavior and associated intentionality, or in some cases, meeting frequency thresholds, as identified in the POMAQ, led to a designation of misuse or abuse in Study 3033-1.

In the context of Study 3033-1, "***addiction***" was defined as ***OUD***, including OUD involving prescription opioids (OUD-P) and/or OUD involving heroin (OUD-H). The OUD outcomes were assessed using the PRISM-5-OP, which was developed from the pre-existing PRISM-5 interview, a computer-assisted, clinician-administered diagnostic interview for DSM-5 disorders that has been extensively validated across different populations with psychiatric and substance use disorders (Hasin et al., 1996; Hasin et al., 2006; Torrens et al., 2004). The PRISM-5-OP instrument was developed for the study due to wide variation in previous methods used to apply DSM-5 to assess OUD among patients prescribed opioids to treat chronic pain, with little evidence for the validity of the different methods and resulting rates. **Study 3033-5** was a cross-sectional study to assess the validity of the PRISM-5-OP in: 1) patients with chronic pain with a current prescription for opioids, and 2) patients in treatment for addiction who also had a prescription for opioids to treat chronic pain (Hasin et al., 2022; Appendix 9.3.1.3).

Study 3033-5 assessed the comparative validity of the following OUD-P outcomes:

- ***Unadjusted measure***: 11 DSM-5 criteria were rated positive if present, without regard for "use as prescribed" or pain.
- ***DSM-5 measure***: withdrawal and tolerance criteria were not rated positive (i.e., were adjusted) if they occurred among participants who used opioids as prescribed, as

defined in DSM-5. The DSM-5 measure may be referred to elsewhere as "DSM-5-OUD definition of OUD".

- ***Pain-adjusted measure***: in addition to the DSM-5 adjustment, DSM-5 behavioral criteria were rated positive only if additional patient information from the PRISM-5-OP instrument indicated that the criteria represented addiction indicators (non-therapeutic intent) rather than treatment of pain (therapeutic intent). The pain-adjusted measure may be referred to elsewhere as "PRISM-5-OP OUD".

Key differences between the DSM-5 and pain-adjusted measures are summarized in Table 2 below.

Table 2: Comparison of Pain-Adjusted and DSM-5 Definitions of OUD-P as Assessed by the PRISM-5-OP in Study 3033-1

Diagnostic Formulation	Criteria	Patient-Reported Information Used to Rate Criteria
PRISM-5-OP pain-adjusted[a] definition of OUD involving prescription opioids	Tolerance and withdrawal	Rated positive only if opioids were taken *other than as prescribed* (e.g., more than prescribed or without a prescription)
	Persistent desire/repeated attempts to quit/cut down	Criteria rated positive *only if* participants made repeated attempts to quit/cut down
	Remaining 8 DSM-5 behavioral criteria	Rated positive *only if* one or more non-therapeutic reason was reported (e.g., to get high, to improve mood, to get to sleep).
PRISM-5-OP DSM-5[b] definition of OUD involving prescription opioids	Tolerance and withdrawal	Rated positive only if opioids were taken *other than as prescribed*.

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders – 5th Edition; OUD = opioid use disorder; OUD-P = opioid use disorder involving prescription opioids; PRISM-5-OP = Psychiatric Research Interview for Substance and Mental Disorders, DSM-5 opioid version.
[a] May be referred to elsewhere as "PRISM-5-OP OUD".
[b] May be referred to elsewhere as "DSM-5-OUD definition of OUD".

The study demonstrated that the pain-adjusted dimensional measures were valid and reproducible, and that the pain-adjusted measures had significantly stronger associations with all validators than the unadjusted or DSM-5 dimensional measures. These findings provide empirical support for the superior validity of the pain-adjusted measures for assessment of OUD in the relevant chronic pain population. When administered by appropriately trained and supervised interviewers, the PRISM-5-OP was found to be acceptable to participants.

More detailed summaries of the instrument validation studies for PMR 3033-1 are provided in Appendix 9.3.1. FDA's evaluation of Studies 3033-3, 3033-4, and 3033-5 can be found at: https://www.fda.gov/media/141350/download.

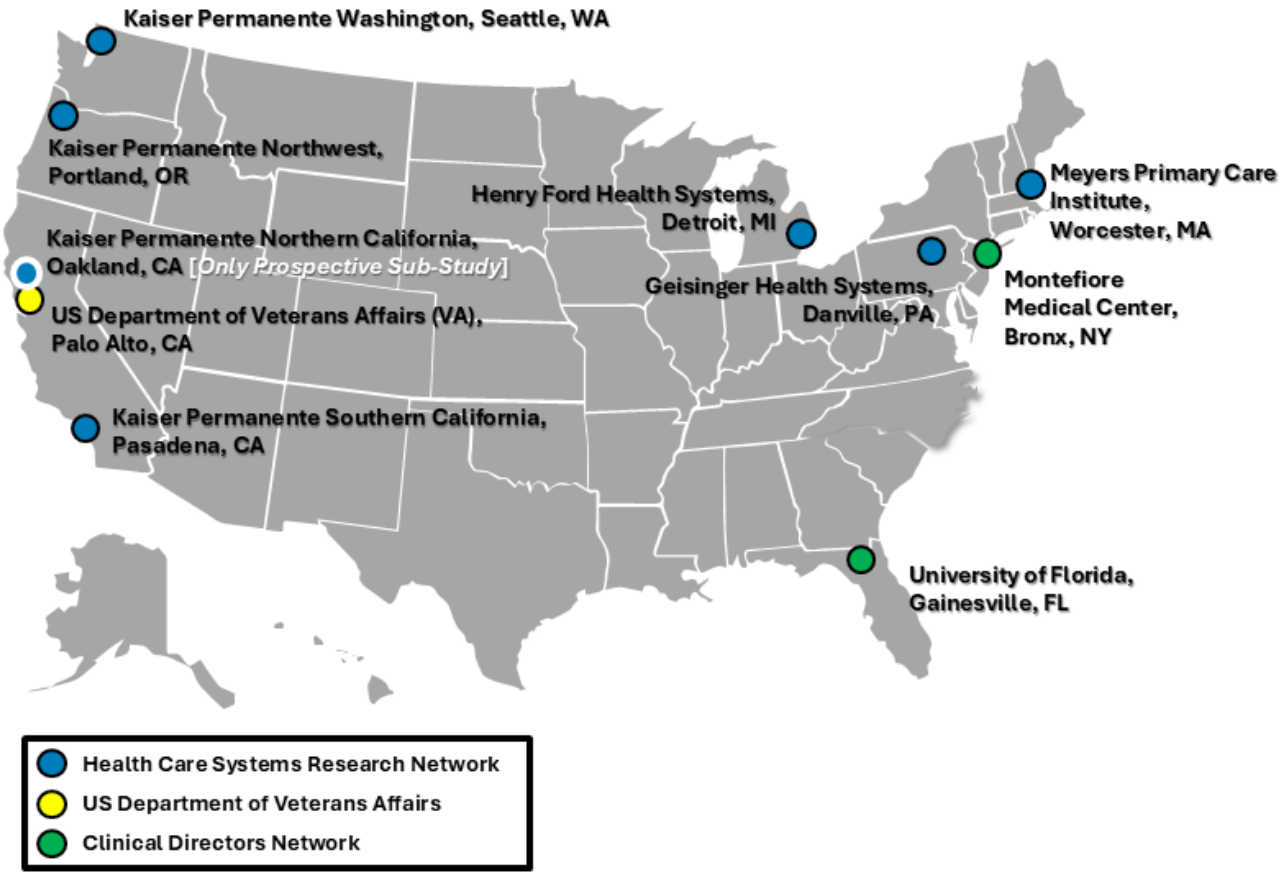
Secondary objectives of Study 3033-1 included:

2. Estimating the incidence of OUD involving prescription opioids (OUD-P), OUD involving heroin (OUD-H), OUD-P without OUD-H, OUD-H without OUD-P, and OUD-P with OUD-H (secondary outcomes).
3. Quantifying the risks of each of the primary and secondary outcomes by potential risk factors (determined *a priori* in the PMR and subject matter experts) including:
   - Predominant type of opioid (ER/LA, IR/SA)
   - Whether the predominant opioid product was an ADF
   - Average daily opioid dose (in MMEs)
   - Duration of prescription opioid use (days)
   - Other clinical factors, including concomitant medication use; medical comorbidities as measured by the Elixhauser comorbidity score (Elixhauser et al., 1998), as well as psychiatric or substance use comorbidities
   - Type of insurance
   - Inpatient stays and emergency department visits
   - Predominant place of care (insured by and receiving care in an integrated delivery system [IDS], only receiving care in an IDS, network/fee-for service)
   - Body Mass Index (BMI)
   - Family history of substance use
   - Demographics including age, sex, race, ethnicity
   - Annual household income
   - Highest level of education
   - Pain and functioning (Brief Pain Inventory [BPI]) (Cleeland & Ryan, 1994)
   - Health and functional status (12-Item Short Form Health Survey [SF-12]) (Ware et al. 1996)
   - Perceived stress (Perceived Stress Scale [PSS]) (Cohen et al., 1983)
   - Social support (Medical Outcome Survey [MOS]) (Sherbourne & Stewart, 1991)
   - Sleep quality (Pittsburgh Sleep Quality Index [PSQI]) (Buysse et al., 1989)
   - Opioid receptor mu-1 (OPRM1) and Cytochrome P450 (CYP3A4 and CYP2D6) enzyme status (optional saliva sample).

5.1.1.2. 3033-1 Prospective Study – Participants

Participants were recruited from 7 Health Care System Research Network (HCSRN) sites, one US Department of Veterans Affairs (VA) site, and 2 sites participating in a Primary Care Practice-Based Research Network (PBRN) (Figure 9). These settings are varied in geographic location, populations served, care delivery, and payment models, and were selected to enhance the diversity of the data. Although additional sites in the Midwest and Southern regions were explored, ultimately none of these sites were able to participate.

Figure 9: Map of 3033-1 Study Sites



CA = California; FL = Florida; MA = Massachusetts; MI = Michigan; NY = New York; OR = Oregon; PA = Pennsylvania; VA = Veteran's Affairs; WA = Washington.

HCSRN sites already shared a common data model; PBRN and VA sites converted relevant local data to a "mirror" common data model to standardize and pool electronic health record (EHR) and claims data. This common data model provided a distinct advantage, in that it enabled efficient recruitment and linkage of participant-reported outcomes to administrative data.

Participants were recruited and data were collected from August 2017 through October 2021. The study included a sample of patients who were 18 – 79 years old at cohort entry, were enrolled in a health plan (HCSRN sites) or regularly receiving care in the health system (VA and PBRNs) for at least 12 months, were able and willing to provide informed consent, were able to complete study measures in English, and who had initiated long-term opioid therapy. The sample was comprised of 2 cohorts:

- ***ER/LA Initiators***: patients who started and refilled a prescription for ER/LA opioids, defined as ≥ 28 days possession of a prescribed ER/LA opioid followed by a subsequent ER/LA prescription, and no ER/LA opioid use in the prior 6 months. Participants in this cohort could have been using IR/SA opioids at the time of enrollment.

- ***LtOT Initiators:*** patients who began using opioid analgesics long-term, defined as ≥ 70 days of opioid possession over a 90-day window with ER/LA and/or Schedule II IR/SA opioids, and no ER/LA or Schedule II IR/SA opioid use in the prior 6 months.

Participants who qualified for both cohorts were categorized as ER/LA Initiators. Although the original intent of the study, as specified in the PMR, was to evaluate patients using long-term ER/LA opioid analgesics, due to changes in clinical practice at the time of study recruitment (as discussed further in Section 6.3), the pool of available participants decreased. Therefore, the eligibility criteria were expanded to include the LtOT Initiators cohort in order to recruit the required number of participants within the mandated timeframes. If a participant qualified for both cohorts at sample selection, priority was given to enrolling the ER/LA Initiators cohort first. However, it should be noted that the study was not designed, nor intended, to compare the relative risk between different opioid formulations (ER/LA or IR/SA). Rather, with the addition of the LtOT cohort, after conducting the risk factor analyses separately by cohort, the modified protocol specified a comparison of baseline characteristics of the 2 cohorts as a sensitivity analysis. If the 2 cohorts were similar (i.e., distribution of the propensity scores for both cohorts overlapped by > 80%) and the findings reasonably convergent, then a sensitivity analysis of incidence and risk factors using a combined cohort was planned to improve study power and precision of estimates. Because the propensity scores did not meet these criteria, the cohorts were analyzed separately.

Participants in both groups were excluded if they were no longer using an ER/LA or IR/SA opioid at the time of recruitment or first interview, if they had cognitive impairment that interfered with their ability to consent or to participate in the interview, or if they were unavailable for 12 months of follow-up, were receiving hospice care, had a diagnosis of a terminal illness in the prior 12 months, had an existing OUD at baseline, or were receiving medication to treat OUD. Note that buprenorphine formulations used to treat OUD (a Schedule III opioid) were excluded as qualifying medications from Studies 3033-1 and 3033-2.

Participation involved a baseline assessment consisting of an in-person or telephone interview, and self- or telephone-administered web-based questionnaires and follow-up assessments, including a 12-month telephone interview and self- or telephone-administered web-based questionnaires at 3, 6, 9, and 12 months. Additional sources of data included EHR and insurance claims data, such as pharmacy utilization, diagnostic codes from ambulatory and inpatient visits, demographics, and a saliva sample from individuals who participated in a genetics sub-study.

A total of 9,601 potential participants were mailed a recruitment letter and subsequent call attempts were made to determine eligibility and interest; 1,088 were subsequently determined to be ineligible. Of the 8,513 who remained eligible, 2,388 (28%) enrolled and 2,222 were included in the analytic dataset (23% of those who were mailed the initial recruitment letter). Not all participants were eligible for all outcome analyses. If a participant had a given outcome at baseline, they were excluded from that outcome analysis but could have been included in analyses of other outcomes. For example, having prescription opioid abuse only (no other outcomes) at baseline excluded someone from the incidence analysis for prescription opioid abuse, but that participant could have been included in the prescription opioid misuse and OUD incidence analyses. Participants who were included in any outcome analyses were designated as “completers.” Completers were similar to “non-completers” (defined as potentially eligible but

who either actively or passively refused participation or were ultimately not eligible for analyses), in observable individual characteristics examined in a selection bias analysis.

5.1.1.3. 3033-1 Prospective Study – Statistical Analyses

Overall and stratified unweighted cumulative incidence were calculated for each of the primary and secondary outcomes. Incidence estimates weighted to the demographics of the targeted population (i.e., demographics for completers and non-completers combined) were also calculated. However, because the weighted incidences were found to be similar to the unweighted estimates, these data are not shown. Within-site correlation was accounted for using the general estimating equations (GEE) method. GEE models with the logit link function were used to estimate risk factors associated with the primary and secondary outcomes in univariate demographically-adjusted (age, sex, race, ethnicity), and fully-adjusted models. Fully-adjusted models included risk factors that were significant at the < 0.10 level in the unadjusted models.

A secondary analysis was performed to examine the past-year incidence of OUD using 2 definitions of OUD-P (pain-adjusted or DSM-5) at different thresholds (≥ 2, ≥ 4, and ≥ 6 criteria; at least mild, moderate to severe and severe, respectively, with ≥ 2 criteria considered “any”). Since a single cut-point was needed, a threshold of ≥ 4 was chosen since it showed the greatest correlation (0.543, CI: 0.492, 0.595) with the composite validator (a variable that combined all the convergent and discriminant validators.) An additional benefit of this cut-point is that it corresponded to the DSM-5 threshold for moderate-to-severe OUD. Data for incidence of OUD presented below (Section 5.1.2.2) include patients with any OUD-H (≥ 2 criteria) and/or OUD-P using the different diagnostic thresholds.

Additional analyses were performed incorporating opioid moiety (the predominant opioid substance participants were using) as a risk factor, including adjustment for opioid moiety in the multivariate analyses.

5.1.2. Summary of 3033-1 Prospective Study Findings

5.1.2.1. 3033-1 Prospective Study – Demographics and Baseline Characteristics

Of the 2,222 participants in the analytic dataset, 978 participants were included in the ER/LA Initiators cohort and 1,244 participants were included in the LtOT Initiators cohort.

A summary of demographic and baseline characteristics of interest (including those found to be statistically significant potential risk factors for at least one primary outcome) is provided in Table 3. Overall, participants in both groups were predominantly ≥ 50 years of age, with a higher proportion of females (57% – 59%); there were also primarily White (78% – 83%) and overweight or obese (71% – 72%). The majority of participants in both cohorts had ≥ 3 pain conditions (most commonly limb/extremity/joint, back, and other pain). Most patients had Elixhauser comorbidity scores ≥ 2, a measure of overall severity of comorbidities, where higher scores indicate higher predicted hospital resource use and mortality. Other medication use (primarily antidepressants and gabapentinoids), as well as comorbidities, were relatively common. The majority of participants in both groups experienced poor sleep, while substantial minorities experienced psychiatric comorbidities, such as major depressive disorder (MDD) or symptoms of generalized anxiety disorder (GAD).

Opioid prescribing in the 2 cohorts differed in terms of predominant opioid formulation, average daily dose, duration of opioid use, and exposure to an ADF, with only a 9.2% overlap in the distribution of the propensity scores for the 2 cohorts. As a result, the cohorts were not combined for the analysis.

Table 3: High-Level Summary of Demographics and Baseline Characteristics of Interest for ER/LA Initiators and LtOT Initiators in 3033-1 – Prospective Study

Demographic/Baseline Characteristic	Source	ER/LA Initiators (N = 978)	LtOT Initiators (N = 1,244)
Age	Self-report/EHR	76% ≥ 50 years of age	72% ≥ 50 years of age
Sex (male / female)	Self-report/EHR	43% / 57 %	41% / 59%
Race	Self-report/EHR	83% White; 9% Black	78% White; 15% Black
Ethnicity	Self-report/EHR	11% Hispanic/Latino	9% Hispanic/Latino
BMI/groups	EHR	71% overweight or obese	72% overweight or obese
Insurance	EHR	20% Medicaid	21% Medicaid
Place of care	EHR	76% care/insurance integrated system; 18% care in integrated system; 6% network/fee-for-service providers	63% care/insurance integrated system; 26% care in integrated system; 10% network/fee-for-service providers
Annual household income	Self-report	64% ≤ $75,000	68% ≤ $75,000
Highest level of education	Self-report	62% any college; 20% high school/GED	56% any college; 25% high school/GED
Hospital visits	EHR	47% ≥ 1 ED visit; 31% ≥ 1 inpatient stay	38% ≥ 1 ED visit; 25% ≥ 1 inpatient stay
Predominant opioid formulation	EHR	60% IR/SA; 40% ER/LA[a]	98% IR/SA; 2% ER/LA
Exposure to ADF	EHR	10%	1%
Predominant opioid	EHR	28% oxycodone; 27% morphine; 19% hydrocodone	58% hydrocodone; 35% oxycodone
Duration of opioid use – Mean (SD)	EHR	132 (45) days	108 (26) days
Average daily MME	EHR	46% < 50 mg/day; 21% ≥ 90 mg/day	86% < 50 mg/day; 3% ≥ 90 mg/day
Pain condition diagnoses	EHR	68% limb/extremity/joint 65% back; 77% other 70% ≥ 3 pain conditions	66% limb/extremity/joint; 59% back; 61% other 59% ≥ 3 pain conditions

Demographic/Baseline Characteristic	Source	ER/LA Initiators (N = 978)	LtOT Initiators (N = 1,244)
Elixhauser CS	EHR	80% CS ≥ 2; 12% CS of 1	76% CS ≥ 2; 14% CS of 1
Pain – Mean (SD)	BPI-SF	5.5 (2.0) pain severity; 6.1 (2.3) pain interference	5.6 (2.0) pain severity; 5.9 (2.5) pain interference
Other medications dispensed (past 12 months)	EHR	61% antidepressants; 47% gabapentinoids; 20% naloxone	50% antidepressants; 40% gabapentinoids; 14% naloxone
Past 3-month Rx misuse/abuse	POMAQ	16% prescription opioid misuse; 5% prescription opioid abuse	18% prescription opioid misuse; 6% prescription opioid abuse
Non-opioid/non-nicotine SUDs	PRISM-5-OP	7% past-year; 29% prior-to-past-year	8% past-year; 34% prior-to-past-year;
History of parental substance use	PRISM-5-OP	44%	47%
Health and social status – Mean (SD)	PSS[b]	15.4 (7.9) stress	14.4 (8.1) stress
	MOS[c]	71.8 (25.6) social support	71.8 (26.3) social support
	SF-12[d]	30.7 (8.7) physical health	32.6 (9.0) physical health
		47.9 (10.9) mental health	48.9 (11.5) mental health
Adverse childhood experiences	ACE	37% ACE ≥ 4; 20% ACE of 0; 16% ACE of 1	37% ACE ≥ 4; 22% ACE of 0; 17% ACE of 1
Psychiatric comorbidities	PRISM-5-OP	15% MDD (past-year); 26% MDD (prior-to-past-year)	13% MDD (past-year); 21% MDD (prior-to-past-year)
	GAD-7	22% probable GAD	24% probable GAD
	PSQI	79% poor sleep	80% poor sleep
	PCL-5	15% probable PTSD	13% probable PTSD
	BPD Screener	9% probable BPD	9% probable BPD

ACE = adverse childhood experiences; ADF = abuse-deterrent formulation; BMI = body mass index; BPD = borderline personality disorder; BPI-SF = Brief Pain Inventory – Short-Form; CS = comorbidity score; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ED = emergency department; EHR = electronic health records; ER/LA = extended-release / long-acting; GAD = generalized anxiety disorder; GAD-7 = Generalized Anxiety Disorder 7-item Scale; GED = general equivalency degree; IR/SA = immediate-release/short-acting; LtOT = long-term opioid analgesic therapy; MDD = major depressive disorder; MME = morphine milligram equivalents; MOS = Medical Outcome Survey; PCL-5 = PTSD Checklist for DSM-5; POMAQ = Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-OP = Psychiatric Research Interview for Substance and Mental Disorders, DSM-5 opioid version; PSQI = Pittsburgh Sleep Quality Index; PSS = Perceived Stress Scale; PTSD = post-traumatic stress disorder; Rx = prescription; SD = standard deviation; SF-12 = 12-item Short Form Health Survey; SUD = substance use disorder.

ER/LA Initiators: initiation of ER/LA opioid therapy that included ≥ 28 days possession of an ER/LA opioid followed by a subsequent ER/LA prescription, and no ER/LA opioid use in the prior 6 months.

LtOT Initiators: initiation of long-term opioid analgesic therapy operationalized as ≥ 70 days of opioid possession over a 90-day window with ER/LA and/or Schedule II IR/SA opioids, and no ER/LA or Schedule II IR/SA opioid use in the prior 6 months.

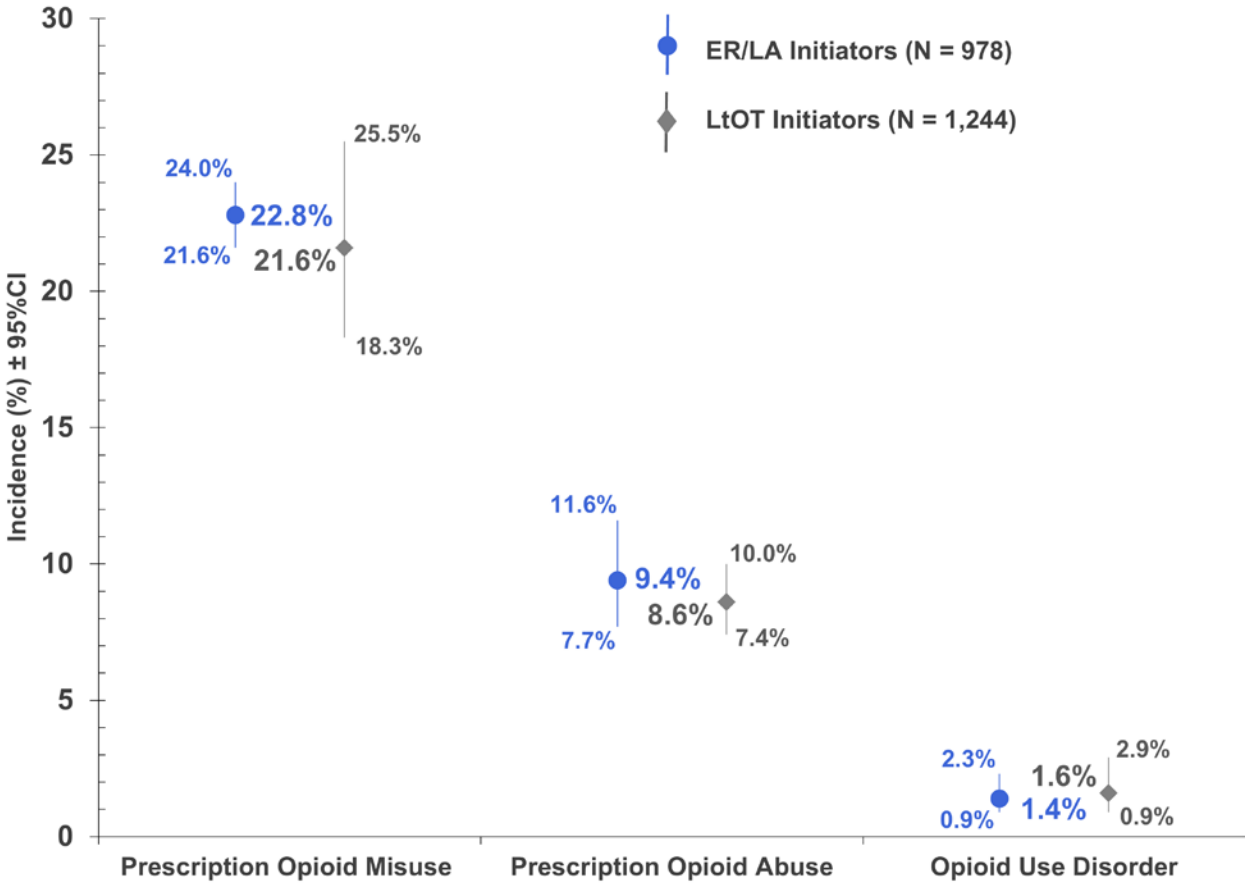
[a.] Changes in ER/LA opioid prescribing led to difficulty recruiting participants using predominantly ER/LA opioids; thus, the ER/LA Initiators group included participants who met eligibility criteria for the cohort but who predominantly used IR/SA opioids.
[b.] PSS range 0 – 40, where a higher score = higher perceived stress.
[c.] MOS range 0 – 100, where a higher score = better health.
[d.] SF-12 range 0 – 100, where a higher score = better health.

Note: Table displays the most common responses for demographics, as well as other baseline characteristics of interest.

5.1.2.2. 3033-1 Prospective Study – Incidence of Misuse or Abuse of Prescription Opioids, or Opioid Use Disorder (Primary Outcomes)

In both cohorts, prescription opioid misuse was the most commonly occurring of the primary outcomes, followed by prescription opioid abuse, and OUD (Figure 10). Despite differences in baseline characteristics with respect to opioid prescribing, the 12-month cumulative incidences of prescription opioid misuse, prescription opioid abuse, or OUD were similar between ER/LA Initiators and LtOT Initiators, with overlapping 95% CIs.

Figure 10: Cumulative 12-Month Incidence (%) ± 95% CI of Prescription Opioid Misuse, Prescription Opioid Abuse, and Opioid Use Disorder in ER/LA Initiators and LtOT Initiators in Study 3033-1 – Prospective Study



CI = confidence interval; ER/LA = extended-release/long-acting; LtOT = long-term opioid analgesic therapy.
ER/LA Initiators: initiation of ER/LA opioid therapy that included ≥ 28 days possession of an ER/LA opioid followed by a subsequent ER/LA prescription, and no ER/LA opioid use in the prior 6 months.
LtOT Initiators: initiation of long-term opioid analgesic therapy, operationalized as ≥ 70 days of opioid possession over a 90-day window with ER/LA and/or Schedule II IR/SA opioids, and no ER/LA or Schedule II IR/SA opioid use in the prior 6 months.

Cumulative incidences of prescription opioid misuse and abuse at 3, 6, and 9 months of follow-up were similar between the cohorts. The incremental incidence of both prescription opioid abuse and misuse (i.e., the difference in cumulative incidence comparing one timepoint to the prior timepoint) decreased over follow-up in both cohorts.

Secondary Analyses:

As noted in Section 5.1.1.3, a secondary analysis was conducted using different thresholds for defining OUD. The definitions of OUD used either the prescription opioid pain-adjusted criteria or prescription opioid DSM-5 criteria (the latter adjusted for tolerance and withdrawal, but not therapeutic use behaviors), as assessed by the PRISM-5-OP. The overall 12-month cumulative incidence of OUD defined as OUD-H (≥ 2 criteria) and/or meeting ≥ 2 prescription opioid pain-

adjusted criteria for OUD-P in the ER/LA Initiators cohort was higher compared to the primary, prespecified analysis (Table 4; i.e., ≥ 4 criteria); the incidence was lower when ≥ 6 pain-adjusted criteria were used as the threshold for OUD-P. The overall unweighted 12-month cumulative incidences of OUD-H and/or meeting ≥ 2, ≥ 4, and ≥ 6 DSM-5 criteria for OUD were higher compared to the respective values obtained with the pain-adjusted criteria. Findings were similar in the LtOT Initiators cohort, in that decreasing or increasing the diagnostic thresholds increased or decreased, respectively, the observed incidences of OUD-P and/or OUD-H, with higher incidences observed using DSM-5 criteria compared to pain-adjusted criteria.

Table 4: Unweighted 12-Month Cumulative Incidence Using Different OUD-P Thresholds for Defining Opioid Use Disorder in 3033-1 – Prospective Study

OUD Criteria	12-Month Cumulative Incidence (95% CIs)	
	ER/LA Initiators (N = 978)	LtOT Initiators (N = 1,244)
Pain-Adjusted[a] DSM-5 Measure		
OUD-H and/or ≥ 2 pain-adjusted OUD-P criteria (any OUD)	8.4% (6.8, 10.2)	5.8% (4.4, 7.7)
Prespecified primary analysis: OUD-H and/or ≥ 4 pain-adjusted OUD-P criteria (moderate-to-severe OUD)	**1.4% (0.9, 2.3)**	**1.6% (0.9, 2.9)**
OUD-H and/or ≥ 6 pain-adjusted OUD-P criteria (severe OUD)	0.4% (0.1, 1.7)	0.9% (0.4, 1.9)
DSM-5[b] Measure		
OUD-H and/or ≥ 2 DSM-5 OUD-P criteria (any OUD)	22.5% (19.0, 26.5)	14.8% (13.0, 16.8)
OUD-H and/or ≥ 4 DSM-5 OUD-P criteria (moderate-to-severe OUD)	5.8% (4.5, 7.3)	3.4% (2.3, 5.1)
OUD-H and/or ≥ 6 DSM-5 OUD-P criteria (severe OUD)	1.1% (0.6, 1.7)	1.5% (0.8, 3.1)

CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual for Mental Disorders, 5th Edition; ER/LA = extended-release/long-acting; LtOT = long-term opioid analgesic therapy; OUD = opioid use disorder; OUD-H = opioid use disorder involving heroin; OUD-P = opioid use disorder involving prescription opioids; PRISM-5-OP = Psychiatric Research Interview for Substance and Mental Disorders, DSM-5 opioid version
ER/LA Initiators: initiation of ER/LA opioid therapy that included ≥ 28 days possession of an ER/LA opioid followed by a subsequent ER/LA prescription, and no ER/LA opioid use in the prior 6 months.
LtOT Initiators: initiation of long-term opioid analgesic therapy, operationalized as ≥ 70 days of opioid possession over a 90-day window with ER/LA and/or Schedule II IR/SA opioids, and no ER/LA or Schedule II IR/SA opioid use in the prior 6 months.
[a] May be referred to elsewhere as "PRISM-5-OP OUD".
[b] May be referred to elsewhere as "DSM-5-OUD definition of OUD".
Note that participants meeting ≥ 2 criteria for OUD-H were included in the outcomes. However, as outlined in Section 5.1.2.3, only a few participants met criteria for OUD-H.

5.1.2.3. 3033-1 Prospective Study – Incidence of Composite Outcome and Opioid Use Disorder Involving Prescription Opioids or Heroin (Secondary Outcomes)

Composite Outcome: The overall unweighted incidence for the composite outcome (12-month cumulative incidence of prescription opioid misuse, prescription opioid abuse, and/or OUD combined) was 24.5% (95% CI: 23.3, 25.7) in ER/LA Initiators and 21.4% (95% CI: 18.8, 24.2) in LtOT Initiators.

OUD-P and/or OUD-H: Only 3 participants had any diagnosis of OUD-H in this study (all 3 in the LtOT Initiators cohort), and 2 of these participants also had OUD-P.

5.1.2.4. 3033-1 Prospective Study – Potential Risk Factors for Prescription Opioid Misuse, Prescription Opioid Abuse, or Opioid Use Disorder

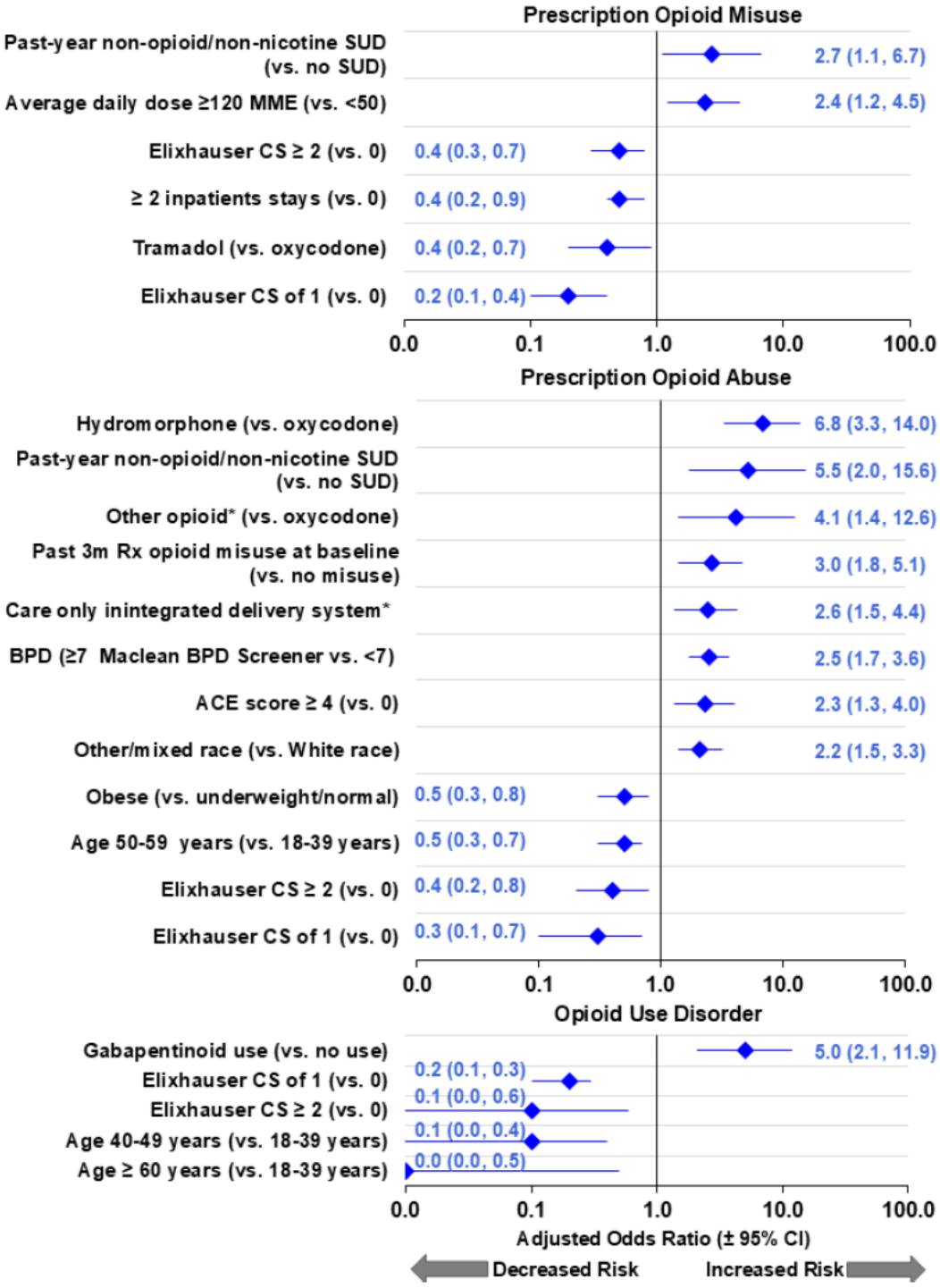
Summaries of potential risk factors associated with the strongest increases or decreases in risk (aOR ≥ 2.0 or ≤ 0.5) for at least one of the primary outcomes (prescription opioid misuse, prescription opioid abuse, or OUD) are provided in Figure 11 (ER/LA Initiators) and Figure 12 (LtOT Initiators). These somewhat arbitrary thresholds were not chosen for their clinical meaningfulness but rather simply because ~ 40 potential risk factors for 3 outcomes in 2 cohorts yield a large number of results. Results highlighted in this section represent potential risk that is at least double or half the reference group. Forest plots of all statistically significant risk factors in the multivariate analysis (i.e., fully-adjusted models) are provided in Appendix 9.1.1.3.

The factor most consistently associated with strongly increased risk of more than one primary outcome (as shown in Figure 11 and Figure 12), was having any non-opioid and non-nicotine SUD in the past year. Other factors related to problematic use or SUDs (e.g., past-3-month prescription opioid abuse or misuse at baseline, past-year OUD-P, prior-to-past-year OUD-P, or prior-to-past-year non-opioid/non-nicotine SUDs) were also associated with a strongly increased risk of at least one outcome. Use of higher daily opioid dose was associated with prescription opioid misuse in the ER/LA Initiators cohort ($\geq$ 120 MMEs per day vs. < 50 MMEs per day) and abuse in the LtOT Initiators cohort (90 – 119 MMEs per day vs. < 50 MMEs per day). Other factors that were associated with increased risk in at least one of the cohorts included predominant use of hydromorphone or codeine, adverse childhood experiences (ACE), having probable bipolar disorder (BPD), gabapentinoid or antidepressant use, or being Black or Hispanic.

The factors associated with strongly decreased risk of more than one outcome (in the ER/LA Initiators cohort only) were having an Elixhauser comorbidity score of 1, 2, or more and being in an older age category (compared to 18 – 39 years), while use of tramadol, obesity, having less than high school education, and emergency department (ED) visits were associated with decreased risk for at least one outcome or cohort.

Several factors were associated with both increased or decreased risk, depending on the outcome and cohort, including inpatient stays, opioid moiety “Other”, and type of medical coverage.

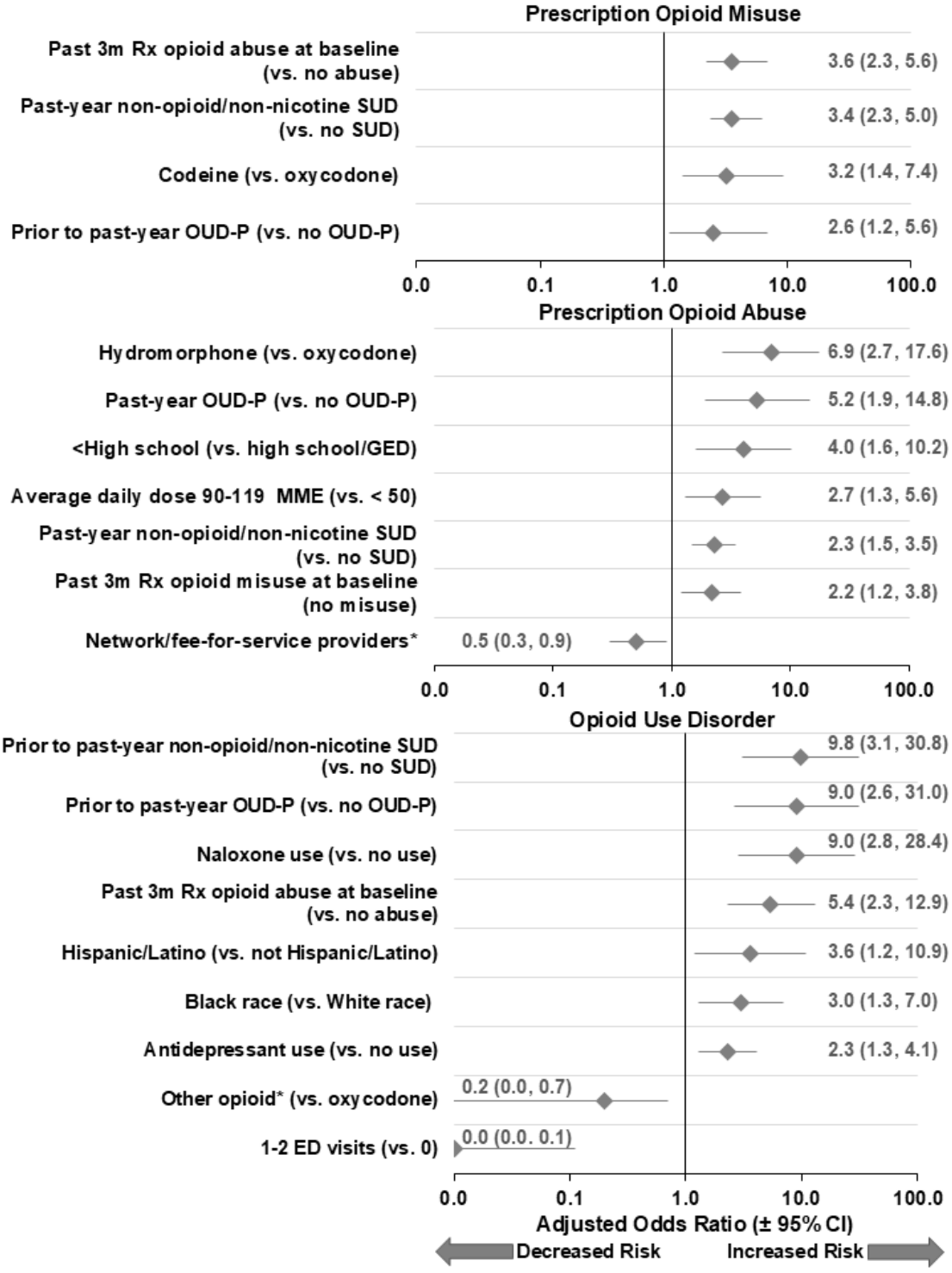
Figure 11: Summary of Potential Risk Factors Associated with Strongly Increased or Decreased Risk (aOR ≥ 2.0 or ≤ 0.5) of Primary Outcomes in ER/LA Initiators from the Fully-Adjusted Model in 3033-1 – Prospective Study



ACE = adverse childhood experiences; aOR = fully-adjusted odds ratio; BPD = borderline personality disorder; CI = confidence interval; CS = comorbidity score; ER/LA = extended-release/long-acting; m = month; MME = morphine milligram equivalents; OUD-P = opioid use disorder involving prescription opioids; Rx = prescription; SUD = substance use disorder.

* vs. insurance and care in an integrated system.

Figure 12: Summary of Potential Risk Factors Associated with Strongly Increased or Decreased Risk (aOR ≥ 2.0 or ≤ 0.5) of Primary Outcomes in LtOT Initiators from the Fully-Adjusted Model in 3033-1 – Prospective Study



CI = confidence interval; ED = emergency department; GED = general equivalency degree; LtOT = long-term opioid analgesic therapy; m = month; MME = morphine milligram equivalents; OUD-P = opioid use disorder involving prescription opioids; Rx = prescription; SUD = substance use disorder.
* vs. insurance and care in an integrated delivery system.

5.1.3. Study 3033-1 – Cross-Sectional Study Objectives and Methodology

5.1.3.1. 3033-1 Cross-Sectional Study – Objective and Outcomes

Because the follow-up period of the prospective study was limited to 1 year, a cross-sectional sub-study was conducted to complement the prospective study by evaluating the outcomes in patients who had been using opioid therapy for ≥ 1 year. Thus, the primary objective of the separate cross-sectional study was to quantify the *prevalence* of and potential risk factors for misuse of prescription opioids, abuse of prescription opioids, and/or OUD among patients on long-term opioid analgesic therapy for at least 1 year, by:

1. Estimating the prevalence of misuse of prescription opioids, abuse of prescription opioids, and OUD (primary outcomes), and a composite of any of these outcomes (secondary outcome).

   Primary and secondary outcomes were determined using the POMAQ and PRISM-5-OP, as described in Section 5.1.1.1 for the prospective study.

2. Estimating the prevalence of OUD-P, OUD-H, OUD-P without OUD-H, OUD-H without OUD-P, and OUD-P with OUD-H (secondary outcomes), defined as described in Section 5.1.1.1 for the prospective study.
3. Quantifying the potential risks of each of the primary and secondary outcomes by potential risk factors determined *a priori*, as described in Section 5.1.1.1 for the prospective study.

5.1.3.2. 3033-1 Cross-Sectional Study – Participants

Participants were recruited from 6 HCSRN sites, one VA site, and 2 sites participating in a PBRN. Participation involved a single assessment consisting of an in-person or telephone interview and self- or telephone-administered web-based questionnaires. Additional sources of data included EHR and insurance claims data. Participants were included if they were regularly using prescription opioids for analgesia for ≥ 12 months prior to enrollment, defined as at least 275 days covered by opioid prescriptions with at least 1 prescription for an ER/LA opioid. Other inclusion/exclusion criteria, other than the requirement to be available for 12 months, were similar to those described for the prospective study (Section 5.1.1.2).

Participants were recruited and data for the cross-sectional study were collected from September 2017 through February 2019.

A total of 5,333 potential participants were sampled for recruitment, received invitation letters, and follow up phone contact attempts. Of the 4,673 who were not determined to be ineligible, 1,212 (26%) enrolled, completed the primary outcome measures, and were included in the analyses (23% of those who were sent a recruitment letter).

5.1.3.3. 3033-1 Cross-Sectional Study – Statistical Analyses

Statistical methods were similar to those of the prospective study, as described above (Section 5.1.1.3). As in the prospective study, weighted prevalence estimates were similar to the unweighted estimates and therefore the data are not shown.

5.1.4. Summary of 3033-1 Cross-Sectional Study Findings

5.1.4.1. 3033-1 Cross-Sectional Study – Demographics and Baseline Characteristics

A summary of demographic and baseline characteristics of interest for the 1,212 included participants in the cross-sectional study is provided in Table 5 (including those found to be statistically significant potential risk factors for at least one primary outcome).

Similar to in the prospective study, participants were primarily older (≥ 50 years of age), White, and overweight or obese, with a slightly higher proportion of females. Participants were predominantly using ER/LA opioids, with the majority using ≥ 50 MMEs per day. Most participants had more than one pain diagnosis (primarily back and limb/extremity/joint pain) and had Elixhauser comorbidity scores ≥ 2. As with the prospective study participants, concomitant medications (primarily antidepressants, sedative hypnotics, and muscle relaxers) and psychiatric comorbidities were common.

Table 5: High-Level Summary of Demographic and Baseline Characteristics of Interest for Participants in 3033-1 – Cross-Sectional Study

Demographic/Baseline Characteristic	Source	Summary of Data (N =1, 212)
Age	Self-report/EHR	~ 80% ≥ 50 years of age
Sex (male / female)	Self-report/EHR	43 / 57%
Race	Self-report/EHR	74% White; 12% Black; 10% unknown
Ethnicity	Self-report/EHR	5% Hispanic
BMI/groups	EHR	~ 59% overweight or obese
Insurance	EHR	43% Medicare; 23% Medicaid
Annual household income	EHR	~ 60% ≤ $50,000/year
Education	Self-report	58% any college; 24% High school/GED
Hospital visits	EHR	66% no ED visits; 76% no inpatient visits
Predominant opioid formulation	EHR	66% predominantly ER/LA
Exposure to ADF	EHR	18%
Predominant opioid used	EHR	37% morphine; 28% oxycodone
Average daily MME	EHR	~ 80% using ≥ 50 mg/day; > 50% ≥ 90 mg/day
Pain condition diagnoses	EHR	95% ≥ 1 pain diagnosis 59% back pain 57% limb/extremity/joint pain or arthritis 15% fibromyalgia
Elixhauser CS	EHR	78% CS ≥ 2

Demographic/Baseline Characteristic	Source	Summary of Data (N =1, 212)
Pain severity/interference – Mean (SD)	BPI-SF	5.7 (1.9) pain severity; 5.8 (2.4) pain interference
Health and social status – Mean (SD)	PSS[a] MOS[b] SF-12[c]	15.1 (8.2) perceived stress 70.3 (26.7) social support 30.9 (8.4) physical health 47.9 (11.5) mental health
Other medications dispensed(past 12 months)	EHR	62% antidepressants; 40% sedative-hypnotic 38% muscle relaxers 13% naloxone 9% antipsychotics
Non-opioid/non-nicotine SUDs	PRISM-5-OP	30% prior to past year; 5% current
History of parental substance use	PRISM-5-OP	47%
Psychiatric comorbidities	PSQI GAD-7 ASRS PCL-5 PRISM-5-OP	80% poor sleep quality 26% probable GAD 16% ADHD 15% probable PTSD 14% MDD

ADF = abuse-deterrent formulation; ADHD = attention-deficit/hyperactivity disorder; ASRS = Adult ADHD Self-Report Scale; BMI = body mass index; BPI=SF = Brief Pain Inventory – Short-Form; CS = comorbidity score; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ED = emergency department; EHR = electronic health records; ER/LA = extended-release/long-acting; GAD-7 = Generalized Anxiety Disorder 7-item Scale; GED = general equivalency degree; MDD = major depressive disorder; MME = morphine milligram equivalents; MOS = Medical Outcome Survey; PCL-5 = PTSD Checklist for DSM-5; PRISM-5-OP = Psychiatric Research Interview for Substance and Mental Disorders, DSM-5 opioid version; PSQI – Pittsburgh Sleep Quality Index; PSS = Perceived Stress Scale; PTSD = post-traumatic stress disorder; SD = standard deviation; SF-12 = 12-item Short Form Health Survey; SUD = substance use disorder.

Note: Table displays the most common responses for demographics, as well as other baseline characteristics of interest.

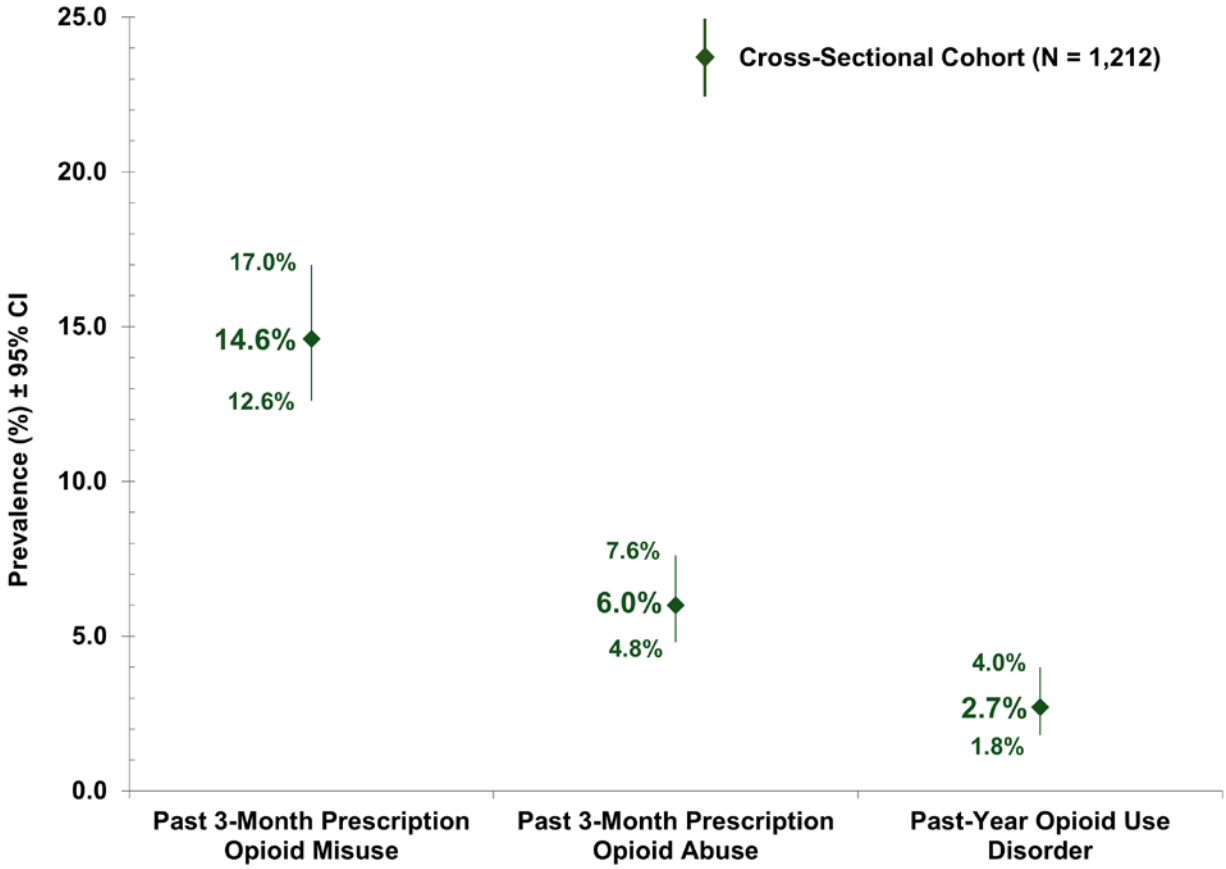
[a] PSS range 0 – 40, where a higher score = higher perceived stress.
[b] MOS range 0 – 100, where a higher score = better health.
[c] SF-12 range 0 – 100, where a higher score = better health.

5.1.4.2. 3033-1 Cross-Sectional Study – Prevalence of Prescription Opioid Misuse, Prescription Opioid Abuse, or Opioid Use Disorder (Primary Outcomes)

The past-3-month prevalence estimates of prescription opioid misuse or abuse, or past-year prevalence of OUD (along with 95% CIs) for the cross-sectional cohort (participants using opioid analgesics ≥ 1 year) are shown in Figure 13. As in the prospective study, prescription

opioid misuse was the most commonly occurring primary outcome, followed by prescription opioid abuse, and then OUD.

Figure 13: Unweighted Prevalence (%) ± 95% CI of Prescription Opioid Misuse, Prescription Opioid Abuse, or Opioid Use Disorder in Study 3033-1 – Cross-Sectional Study



CI = confidence interval.

Secondary Analysis:

As in the prospective study, past-year prevalence of OUD was explored using different diagnostic thresholds for pain-adjusted outcomes. Results demonstrated that using different thresholds for OUD using the pain-adjusted measures altered the prevalence of OUD relative to the primary outcome (≥ 4 criteria):

- 1.0% (95% CI: 0.5, 1.8) for ≥ 6 pain-adjusted DSM-5 criteria for the OUD diagnoses
- 8.5% (95% CI: 6.5, 11.1) for ≥ 2 pain-adjusted DSM-5 criteria for the OUD diagnoses.

Using DSM-5 criteria instead of pain-adjusted criteria resulted in a higher prevalence of OUD:

- ≥ 2 criteria: 27.1% (95% CI: 23.5, 31.2)

- ≥ 4 criteria: 6.3% (95% CI: 4.3, 9.1)
- ≥ 6 criteria: 2.1% (95% CI: 1.3, 3.4).

5.1.4.3. 3033-1 Cross-Sectional Study – Prevalence of Composite Outcome and Opioid Use Disorder Involving Prescription Opioids or Heroin (Secondary Outcomes)

Composite Outcome: The overall unweighted prevalence for the composite outcome (past-3-month prescription opioid misuse, past-3-month prescription opioid abuse, and/or past-year OUD) was 18.3% (95% CI: 16.2, 20.7).

OUD-P and/or OUD-H: There were only 2 participants who met criteria for OUD-H. Both participants also met criteria for OUD-P.

5.1.4.4. 3033-1 Cross-Sectional Study – Risk Factors for Primary and Secondary Outcomes

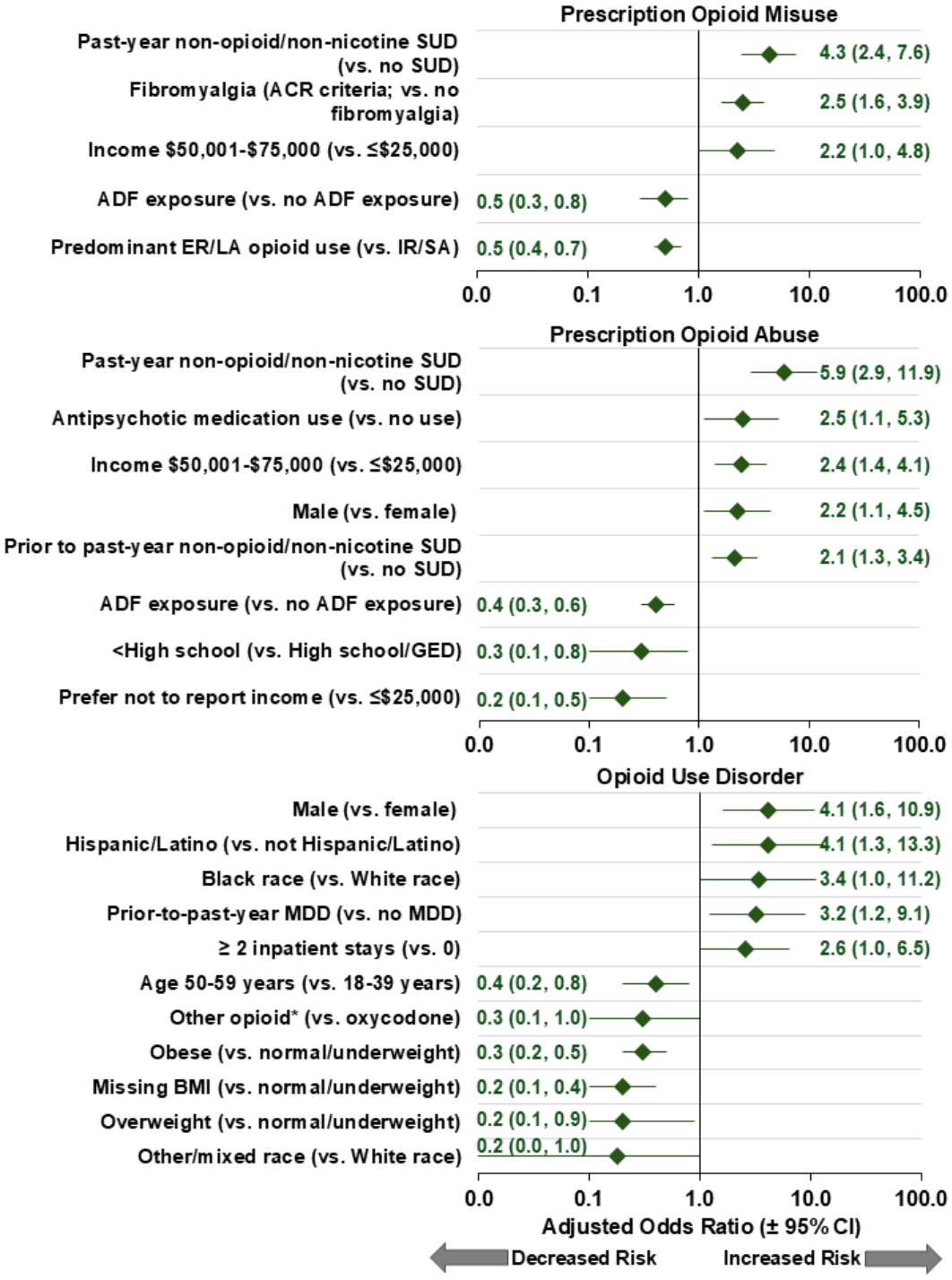
5.1.4.4.1. Potential Risk Factors for Past-3-Month Prescription Opioid Misuse, Prescription Opioid Abuse, or Past-Year Opioid Use Disorder

A summary of potential risk factors associated with the strongest increases or decreases in risk (aOR ≥ 2.0 or ≤ 0.5) for at least one of the primary outcomes is provided in Figure 14. Forest plots for all statistically significant risk factors for the primary outcomes in the fully-adjusted models are provided in Appendix 9.1.2.1.

As in the prospective study, having any past-year non-opioid/non-nicotine SUD was associated with strongly increased risks for prescription opioid misuse and abuse (along with prior to past-year non-opioid/non-nicotine SUDs for abuse). Having an annual income of $50,000 – $75,000 (relative to ≤ $25,000) was associated with both prescription opioid misuse and abuse, while being male was strongly associated with prescription opioid abuse and OUD. Fibromyalgia and antipsychotic medication use were potential risk factors for prescription opioid misuse and abuse, respectively, while being Black or Hispanic, having prior to past-year major depression, and having ≥ 2 inpatients stays were potential risk factors for OUD.

Exposure to ADFs (i.e., opioid products formulated with inactive ingredients intended to make the product more difficult to manipulate for misuse and abuse) was associated with a decreased risk for both prescription opioid misuse and abuse. Predominant use of an ER/LA opioid was associated with decreased risk for prescription opioid misuse. Other factors associated with a decreased risk for at least one outcome included having less than high school education, preferring not to report income, being of other/mixed race, using an “other” opioid, or being obese, overweight or having a missing BMI.

Figure 14: Summary of Factors Associated with Strongly Increased or Decreased Risk (aOR ≥ 2.0 or ≤ 0.5) of Primary Outcomes from the Fully-Adjusted Model in 3033-1 – Cross-Sectional Study



ACR = American College of Rheumatology; ADF = abuse-deterrent formulation; aOR = fully-adjusted odds ratio; BMI = body mass index; CI = confidence interval; ER/LA = extended-release/long-acting; GED = general equivalency diploma; IR/SA = immediate-release/short-acting; MDD = major depressive disorder; SUD = substance use disorder.
Note: The number and proportion of missing data in the covariates of interest was small (ranging from 0.1% to 26%). A summary of differences for the multiple imputation sample compared to the fully-adjusted models is provided in Appendix 9.1.2.

5.1.5. Study 3033-1 – Discussion and Interpretation

The primary objective of Study 3033-1 was to quantify the serious risks of prescription opioid misuse, prescription opioid abuse, and/or OUD among patients with chronic pain using long-term opioid analgesic therapy. Study 3033-1 consisted of a large, observational, prospective cohort study with 1 year of follow-up among patients with newly initiated long-term opioid analgesic therapy to estimate the incidence of misuse or abuse of prescription opioids or OUD, and a cross-sectional study among patients who had used opioid therapy for at least 1 year to estimate the prevalence of misuse or abuse of prescription opioids or OUD. In secondary analyses in both sub-studies, the impact of using different OUD definitions or different OUD criteria thresholds on incidence or prevalence rates was examined. Both the prospective and cross-sectional studies included an evaluation of potential risk factors for prescription opioid misuse, prescription opioid abuse, and OUD.

In both the prospective and cross-sectional studies, participants were generally ≥ 50 years of age, White, and overweight/obese, with multiple comorbidities and concomitant medications. Pain diagnoses consisted primarily of back pain and joint/limb/extremity pain. Approximately 10% and 1% of ER/LA and LtOT Initiators in the prospective study had been exposed to an ADF, respectively, compared to 18% in the cross-sectional study. While oxycodone and morphine were the most common opioids used in both the cross-sectional study and the ER/LA Initiators cohort of the prospective study, LtOT Initiators predominantly used hydrocodone, followed by oxycodone. Daily MMEs were also higher among cross-sectional study participants (~ 80% using ≥ 50 MMEs per day; 50% ≥ 90 MMEs per day) compared to the ER/LA Initiators (46% < 50 MMEs per day; 21% ≥ 90 mg/day) and particularly to LtOT Initiators (86% < 50 MMEs per day; 3% ≥ 90 MMEs per day).

In both the prospective and cross-sectional studies, which used the same instruments (POMAQ and PRISM-5-OP), adverse opioid-related outcomes occurred with long-term opioid use, and consisted mainly of prescription opioid misuse. As outlined in Appendix 9.1.1, participants were categorized with prescription opioid misuse if they reported just one misuse intention related to their behavior (e.g., use of more than one doctor/pharmacy in order to ensure adequate supplies for pain relief, taking more than prescribed to sleep better). The cumulative 12-month incidences of prescription opioid misuse and abuse were similar between ER/LA Initiators (22.8% misuse; 9.4% abuse) and LtOT Initiators (21.6% misuse; 8.6% abuse) in the prospective study. The 12-month cumulative incidences of OUD were also similar between the ER/LA Initiators and LtOT Initiators cohorts (1.4% and 1.6%, respectively), despite differences in use of ER/LA vs. IR/SA opioids and daily MMEs. In the cross-sectional study, prevalences of past-3-month prescription opioid misuse and abuse were 14.6% and 6.0%, respectively, while past-year prevalence of OUD was 2.7%. Secondary analyses showed estimates that differed from the primary analysis, which used ≥ 4 OUD criteria (higher or lower depending on the number of criteria required and type of definition [pain-adjusted vs. DSM-5]). In one of the estimates (using ≥ 2 DSM criteria), the incidence of OUD differed between ER/LA and LtOT Initiators (22.5% vs. 14.8%, respectively).

An important and consistent risk factor for the primary outcomes in the prospective and cross-sectional studies was the history or presence of an SUD (i.e., depending on the study, cohort, and outcome, indicators may have comprised past-year non-opioid and non-nicotine SUDs, past-year OUD-P, prior-to-past-year non-opioid and non-nicotine SUDs, or prior-to-past-year OUD-P). Other risk factors varied by study, outcome, and cohort. Use of ER/LA opioids was not found to be a risk factor for prescription opioid misuse, prescription opioid abuse, or OUD in either study in the models that were fully adjusted for all confounders and covariates. In the cross-sectional study, predominant

use of an ER/LA opioid was associated with a significantly decreased risk for prescription opioid misuse, and exposure to ADFs was associated with a decreased risk for both prescription opioid misuse and abuse. These findings are important from a risk management perspective, to inform prescribers regarding appropriate use of long-term opioid analgesic therapy and monitoring for at-risk patients.

5.1.5.1. Relationship of Study 3033-1 Results to Previous Findings

No prospective study of incident OUD, diagnosed using DSM-5 criteria, among chronic pain patients was identified in the literature. Published reviews of opioid abuse or dependence among patients receiving opioids for chronic pain estimate that incidence ranges between 0.19% and 4.7% (Fishbain et al., 2008; Higgins et al., 2018; Minozzi et al., 2013; Noble et al., 2008). The Study 3033-1 outcomes of pain-adjusted moderate OUD-P and/or OUD-H fall within this range; however, DSM-5 rates were 3-to 5-times higher.

Prevalence of various aberrant opioid use behaviors has been more commonly reported. Using a variety of techniques, Vowles et al. (2015) calculated average prevalence rates of misuse of 21% – 29%. A large and more recent systematic literature review and meta-analysis, including data up to 2021 for participants (≥ 12 years of age) with non-cancer pain (≥ 3 months) who were treated with opioid analgesics, reported a pooled prevalence of "aberrant behaviors" (some of which may overlap with the misuse definition in Study 3033-1) of 29.6% (95% CI: 22.1, 38.3) (Thomas et al., 2024). These rates more closely approximate the incidence of misuse found in the 3033-1 prospective study; the prevalence of misuse was lower (14.6%) in the cross-sectional study.

Thomas et al. (2024) also evaluated a category of behaviors referred to as "signs and symptoms of dependence and OUD", which may have some overlap with the abuse category in Study 3033-1, but also with the OUD category (e.g., presence of tolerance and withdrawal, craving). In this study, the pooled prevalence of signs and symptoms of dependence and OUD was 12.4% (95% CI: 4.3, 30.7), twice the rate of prescription opioid abuse found in the cross-sectional study.

Thomas et al. (2024) identified "dependence and OUD" via DSM or ICD-10 diagnostic criteria/codes and found a pooled prevalence of 9.3% (95% CI: 5.7, 14.8), while Vowles et al. (2015) calculated average prevalence rates of "addiction" of 8% – 12% (range across 10 studies: 0.7% – 23.0%). Both of these estimates were much higher than the pain-adjusted main outcome in the cross-sectional study (2.7%) and lower than the secondary estimate obtained using ≥ 2 DSM-5 criteria as the diagnostic threshold (27.1%). An Australian examination of SUDs among chronic non-cancer pain patients treated with opioids found rates of 29.4% and 20.8%, using DSM-5 criteria (≥ 2 criteria) with and without tolerance/withdrawal, respectively (Degenhardt et al., 2015). This estimate is relatively similar to the secondary findings in Study 3033-1.

Thomas et al. (2024) highlight the considerable heterogeneity among studies (published between 1985 and 2022) across outcomes and the high variation in relation to classification and measurement of outcomes, diagnostic tool (or method of assessment), and study setting. As stated in the introduction, this variability motivated the need for Study 3033-1. However, the estimates obtained in the 3033-1 studies may vary from other study findings due to additional factors such as changes in prescribing practices, state-level prescription drug monitoring programs, and broader awareness around the importance of reducing problematic opioid use (Section 6.3). In both 3033-1 studies, participants were recruited after the release of the 2016 Centers for Disease Control and Prevention (CDC) Guidelines (Dowell et al., 2016), during a time when states introduced policies aimed to reduce inappropriate

prescribing and after some health systems had instituted controls that prevented risky prescribing (Kuntz et al., 2020; Losby et al., 2017; Schuchat et al., 2017). Thus, there may have been a reduction of susceptible patients if those developing problematic opioid use were taken off opioids. In addition, in this later study period, prescribers may have become more attuned to the risks of OUD and therefore may have prescribed primarily to patients at lower risk of developing OUD or problematic opioid use.

Many of the potential risk factors identified in the 3033-1 studies were consistent with those observed in other studies. Factors commonly recognized as risk factors for problematic opioid use include male sex, white race, young age, psychotropic medication use, genetics, mood disorders, smoking, childhood adversity, pain, non-functional status due to pain, exaggeration of pain (catastrophizing), unclear etiology for pain, poor social support, psychological stress, psychological trauma, psychological disease, preadolescent sexual abuse, history of legal problems, and personal or family history of SUDs (Boscarino et al., 2010; Fishbain et al., 2008; Martel et al., 2020; Reid et al., 2002; Volkow et al., 2019; Webster & Webster, 2005; Webster, 2017). A review of 54 studies identified risk factors for misuse of prescription opioids, but the definition of misuse included any aberrant drug behavior, opioid abuse, or any component of the definitions of opioid addiction or dependence from the DSM-5 (Cragg et al., 2019). Factors associated with problematic opioid use in this review included current or previous substance use, tobacco use/abuse, illicit drug use history, any mental health diagnosis, depression or anxiety, IR/SA opioid use, younger age, and male sex.

Contrary to studies that report increased risk of adverse health outcomes with high-dose opioids (defined as misuse, abuse, addiction, overdose, and death) (Coyle et al., 2018), there was no association between dose and misuse or abuse of prescription opioids or OUD in the fully-adjusted models of the cross-sectional study. However, in the prospective study, average dose of ≥ 120 MMEs per day (vs. < 50) was a potential risk factor for prescription opioid misuse in ER/LA Initiators, while average dose of 90 – 119 MMEs per day (vs. < 50) was a potential risk factor for prescription opioid abuse in LtOT Initiators.

5.2. PMR 3033-2: Incidence and Predictors of Opioid Overdose and Death among Users of Opioid Analgesics as Measured by Diagnoses and Death Records – A Retrospective Database Study

5.2.1. Study 3033-2 – Objectives

The **Primary Objectives** of Study 3033-2 were:

1. In data available through December 31, 2017, estimate the cumulative risk and the incidence rate of OOD at various intervals following a Cohort Start Date. Cohort Start Dates ran from October 1, 2006, through December 31, 2016.
    a. Conduct a sensitivity analysis with follow-up through drug discontinuation only.
2. Identify opioid exposure measures and other covariates that may be risk factors for the occurrence of OOD.

Secondary Objectives were to:

1. Describe long-term opioid users in terms of treatment, personal, and other characteristics, as ascertained at the Cohort Start Date.
2. Present the prevalence of opioid treatment and of all covariates at regular intervals during follow-up.
3. Estimate the cumulative risk and the overall incidence rate of OOD from Cohort Start Date through regular intervals during follow-up in strata defined by the risk factors examined in primary objective 2 and calculate the risk difference and incidence rate ratio through the end of each follow-up interval.
4. Identify a population identical to that used for the primary objectives, except that a dispensing of a Schedule II opioid was permitted in the interval from 183 through 31 days before onset of the opioid treatment episode leading to designation of long-term use. Estimate the cumulative risk and incidence rate of OOD at regular intervals during follow-up.
5. Estimate the cumulative risk of OOD not designated as intentional at regular intervals during follow-up. This was an exploratory analysis.
6. Compare covariate-adjusted cumulative risk of OOD between persons who (a) switched to/added on an ER/LA opioid and those who (b) switched to/added a new IR/SA opioid following a period of stable IR/SA-only therapy. For persons in groups (a) and (b), describe the cohorts in terms of available covariates. Estimate cumulative risks and incidence rates through two censoring points: (1) discontinuation or change of the treatment regimen that qualified individuals as members of the switch/add cohort; (2) through all available follow-up. Present risk differences and incidence rate ratios.
7. Conduct a partial assessment of validity of International Classification of Diseases 10th Revision (ICD-10) codes to identify OOD and determine intentionality. (Note: this objective was evaluated because validation Study 3033-6 was conducted using ICD-9-CM codes; however, ICD-10 came into effect near the end of the data collection period, in 2015).

5.2.2. Study 3033-2 – Design and Methodology

Study 3033-2 sought to implement the goals of PMR 3033-2, while respecting the following aims:

- Complete enumeration and complete follow-up over several years of large, well-defined populations in diverse settings.
- Extensive, passively collected data on:
  - Personal characteristics (demographics and medical history)
  - Prescription medications (date dispensed, chemical, dose, quantity)
  - Medical care (date, nature, provider type, assigned diagnoses)
  - Mortality.
- Monitoring of ongoing medication use and medical care.
- Analysis of:

    - Outcomes captured in medical care and mortality as predicted by features ascertained before the beginning of follow-up, including:
        - Personal characteristics
        - Opioid dose, quantity, and formulation dispensed in the 90 days before the start of follow-up.
- Partnering with research organizations with published experience in:
    - Pharmacoepidemiology studies conducted in collaboration with FDA, the NIH, and non-governmental entities.

5.2.2.1. Study 3033-2 – Source Populations

The research centers from which participants were derived included Vanderbilt University Medical Center (VUMC; collaborating with TennCare, the Tennessee state Medicaid program), Kaiser Permanente Northwest (KPNW, a regional non-profit health care organization), HealthCore (more recently re-named Carelon but referred to herein as HealthCore, the entity's name during the study), and Optum (research groups affiliated with national commercial health insurers).

5.2.2.2. Study 3033-2 – Outcome

OOD consisted of:

- Opioid overdose events identified in EHRs and insurance claims data, and
- Deaths with a principal or contributing cause of death indicated as opioid overdose in data maintained by the US NDI. Only the first OOD event occurring during cohort follow-up was considered an outcome. An exploratory investigation looked at presumably unintentional overdoses, defined as the subset of OOD for which available ICD codes did not indicate intentional self-harm.

The rule for determination of OOD was based on the results of a validation study conducted under PMR 3033. **Study 3033-6** used claims databases to examine algorithms to identify and classify OOD events; the activity relevant to 3033-2 was a definition based solely on coded medical terminology. Although Study 3033-6 investigators examined a wide range of plausible enhancements to a pre-existing algorithm that consisted of using codes specific to "opioid toxicity," none of the enhancements provided improved discrimination in a test against manual chart review. Therefore, Study 3033-6 proved to be a validation study of the existing algorithm. As a secondary objective, Study 3033-6 provided a means of identifying OOD that was the result of intentional self-harm (referred to by the shorthand term "intentionality" elsewhere in this document). A more detailed summary of the algorithm validation Study 3033-6 is provided in Appendix 9.3.2.1.

Study 3033-7 developed and assessed an algorithm for identifying OUD in populations similar to those planned for inclusion in Study 3033-2. Clinical experts aided the researchers in identifying many hundreds of temporal sequences of health care utilization, medication dispensing, claims diagnosis, and test results that might be indicative of misuse, abuse, and OUD. These results were fashioned into a best-discriminating algorithm with a variety of multivariable statistical procedures (least absolute shrinkage and selection operator, and classification and regression trees) to predict chart-review adjudications. The resulting algorithm, when tested in a validation sample and in

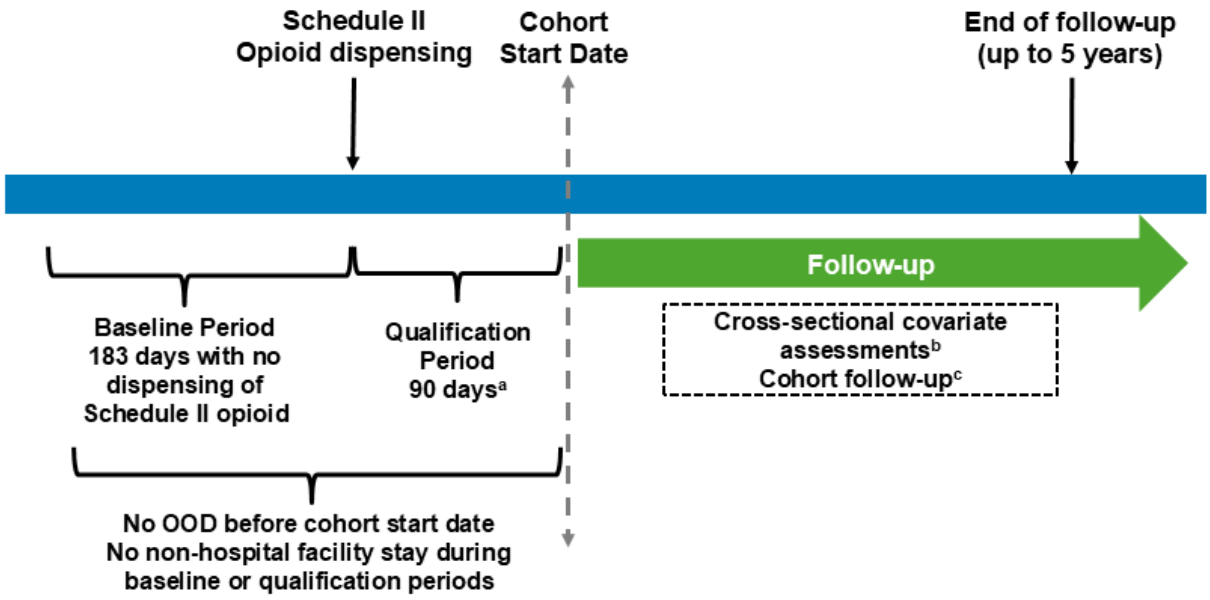
different databases, did not achieve sensitivity and specificity that could justify its use for the assessment of OUD in patients using long-term opioid analgesic therapy.

5.2.2.3. Study 3033-2 – Overall Design

Study 3033-2 was a retrospective cohort study of new long-term users of Schedule II opioids identified from pharmacy dispensings. Cohort accrual ran from the earliest cohort eligibility date in 2006 through December 2016, and follow-up continued to the end of 2017.

Figure 15 provides an overview of the Study 3033-2 design and illustrates how opioid recipients were selected for the study and followed for the outcome of OOD. Schedule II opioid dispensings to individuals between October 2006 and December 2016 were identified. To identify "new use", it was confirmed that the person was enrolled in the data source for 6 months prior to this dispensing and did not have a Schedule II opioid dispensing during that time. This single cohort was followed for up to 5 years with additional censoring for a number of administrative reasons. At periodic points, the cohort was characterized, using covariates that were also assessed at cohort entry. This design allowed assessment of changes in cohort makeup during follow-up.

Figure 15: Overview of Restrospective Study 3033-2 Design



a. Having 70 days of Schedule II opioid supply during 90 days was the threshold for qualification.
b. Covariate assessments continued annually through cohort follow-up.
c. Other events that terminated follow-up: OOD, death, non-hospital facility stay.
(other than for treatment of substance abuse), day preceding 80th birthday, end of study period (Dec 31, 2017).

5.2.2.4. Study 3033-2 – Eligibility Criteria

Inclusion criteria included:

- *Prior enrollment* in one of the participating health care systems with full coverage for at least 273 days, consisting of 183 days to define a Baseline Period plus 90 days for a Qualification Period.
- *New use* of Schedule II opioids. The Qualification Period began with a dispensing of a Schedule II opioid with no previous Schedule II opioid dispensing in the preceding 183 days.[a]
- *Long-term use:* at least 70 days of Schedule II opioid dispensed in the 90 days of the Qualification Period.
- *Age* between 18 and 79 years (inclusive) at Cohort Start Date, which was the last day of the Qualification Period.

Exclusion criteria included:

- *Opioid overdose* during the Baseline or Qualification Periods.
- *Non-hospital institutional stay* during the Baseline or Qualification Periods

Past or current use of Schedule III (other than hydrocodone), IV or V drugs was not an exclusion criterion.

If a potential cohort member qualified for cohort entry more than once, the first qualifying Cohort Start Date was selected as the beginning of cohort membership.

5.2.2.5. Study 3033-2 – Cohort Follow-up

Follow-up began on the Cohort Start Date, which was the last day of the Qualification Period, or equivalently, the 90th day counting from the date of the first dispensing of a Schedule II opioid that marked the beginning of the Qualification Period.

Follow-up continued through the Cohort End Date, defined as the earliest of the following days, with no required minimum follow-up time:

- The date of disenrollment from the site-specific health care system or the end of the study period (December 31, 2017).
- The start date of a non-hospital institutional stay (other than for substance use).
- The day preceding the 80th birthday.
- The date of death.
- The date of occurrence of OOD.

Secondary objective 6 involved the “Switch/Add” study, using subjects identified from the primary cohort, who were then analyzed as a separate, smaller group. Switch/Add study members were kept in the primary cohorts for the other objectives. Among IR/SA opioid recipients with ongoing dispensings of the drug that originally qualified as the principal molecule (see below), indicating a stable treatment

[a] Hydrocodone was reclassified from Schedule III to Schedule II in October 2014; thus, hydrocodone was treated as a Schedule II opioid throughout the study.

regimen, the risk of OOD was compared between users who changed their treatment regimens through the introduction of a new IR/SA opioid, versus those who changed their regimens through the introduction of an ER/LA opioid. Covariates identified for the primary cohort were re-evaluated during the 90 days preceding the Switch/Add date, and MMEs were monitored before and after the Switch/Add date. There was statistical control for covariates ascertained before the Switch/Add date. Dose changes after Switch/Add were taken as integral to treatment regimen changes associated with the Switch/Add.

5.2.2.6. Study 3033-2 – Opioid Exposures

Baseline:

The quantitative exposure measure was total MMEs of opioid dispensed during the 90 days of a Qualification Period. Further measures included the "principal molecule," which was the chemical entity contributing most to the Qualification Period MMEs for each cohort member. Principal molecules were examined as distinct entities for the prediction of OOD and for the same purposes were grouped according to formulation (ER/LA vs. IR/SA).

Follow-up:

During follow-up, opioid exposure measures were monitored to characterize the evolving drug-use profile of the cohort. These measures included the total number of dispensings, the cumulative dose of opioids in MMEs, and the totals of opioid treatment days dispensed (by Schedule [II, III], and formulation, ascertained for the intervals ending at 3, 6, 9, and 12 months for the entire first year, and annually thereafter). The monitoring characterized the cohort at later stages of follow-up. Continued prescription opioid use was *not* a criterion for remaining under observation.

5.2.2.7. Study 3033-2 – Other Baseline Covariates

Other covariates were demographic factors available in insurance files (age, sex, region, calendar year of cohort entry), diagnoses of pain-causing conditions, and diagnoses of mental health conditions (including SUDs).

5.2.2.8. Study 3033-2 – Statistical Analysis

Kaplan-Meier curves and interval estimates of cumulative risk were used to characterize the evolution of risk over time since cohort entry. Incidence rates were calculated through the end of each follow-up interval. Sensitivity analyses were carried out with censoring at first discontinuation of Schedule II opioid therapy.

Analysis of potential risk factors for OOD involved estimates from proportional hazards models adjusted for age, sex, census region, and calendar era of cohort entry. Each of the 4 sites conducted an independent analysis following common specifications. All outcome analyses involved only baseline opioid and covariate values as predictors.

The coordinating center summarized hazard ratios (HRs) by meta-analysis using the Paule-Mandel random-effects estimator with an associated Higgins-Thompson heterogeneity index (range: 0 – 1) (Higgins & Thompson, 2002; Paule & Mandel, 1989). A heterogeneity index > 0.50 connotes meaningful between-site discrepancies. With 4 sites, chance produces in expectation an index value > 0.50 in about 10% of summaries.

Although the PMR mandate for Study 3033-2 was entirely descriptive, the observation of factors influencing risk leads naturally to causal hypotheses. Causal assessment was not the purpose of the study, but the investigators opted to refine the observations and thereby sharpen the hypotheses with limited multivariable analyses. This secondary evaluation sought to identify predictors that operated independently of their correlation with other factors. Mutual adjustment of all covariates by one another has been discouraged for multiply correlated predictors in medical settings (Westreich & Greenland, 2013), and was undertaken here only to identify potential risk factors that were not merely correlates of opioid analgesic dose. Analysis of all potential risk factors together was possible only in the VUMC data, where there were enough OOD events to support the full regression. Other centers undertook a backwards elimination procedure with a p-value for retention of 0.1.

The products of the covariate-adjusted proportional hazards outcome analyses are HRs. An HR is a weighted estimate of the ratio between the statistical parameters for the underlying disease incidence rates in compared populations. For general reading, to interpret an HR as an incidence rate ratio is accurate. HR estimates are given with 95% CIs. P-values are included in Appendix 9.2.1 for reader familiarity and as an occasional tool for sorting HRs. There were no pre-specified hypotheses, and p-values are not statistical tests.

In the Switch/Add analysis, within each site, the 2 cohorts were balanced using inverse probability of treatment weights to account for differences in characteristics present both at the original study baseline and the 90 days preceding the Switch/Add date. The HR between ER/LA and IR/SA was assessed in a proportional hazards model. Additionally, opioid dose after the Switch/Add date was monitored, but not adjusted for, as it would have been a consequence of the Switch/Add decision and therefore an intermediate variable.

5.2.3. Summary of Study 3033-2 Findings

Study findings are presented below according to the order of the study objectives. Cohort characteristics are described under the results for secondary objectives 1 and 2 (refer to Section 5.2.3.2.1 below).

5.2.3.1. Study 3033-2 – Primary Objectives

5.2.3.1.1. Study 3033-2 – Cumulative Risk and the Incidence Rate of Opioid-Involved Overdose or Opioid-Overdose-Related Death (OOD) (Primary Objective 1)

As summarized in Table 6, there were 3,034 first-time OOD events (509 of which were fatal; 16.8%) during 577,234 py of cohort follow-up, in 220,249 cohort members across all sites. The corresponding incidence rate for first-time OOD was 5.3 per 1,000 py (i.e., 3,034 events/577,234 py).

Table 6: Summary of Opioid-Involved Overdose or Opioid-Overdose-Related Death (OOD) Events, Persons, and Person-Times – Study 3033-2

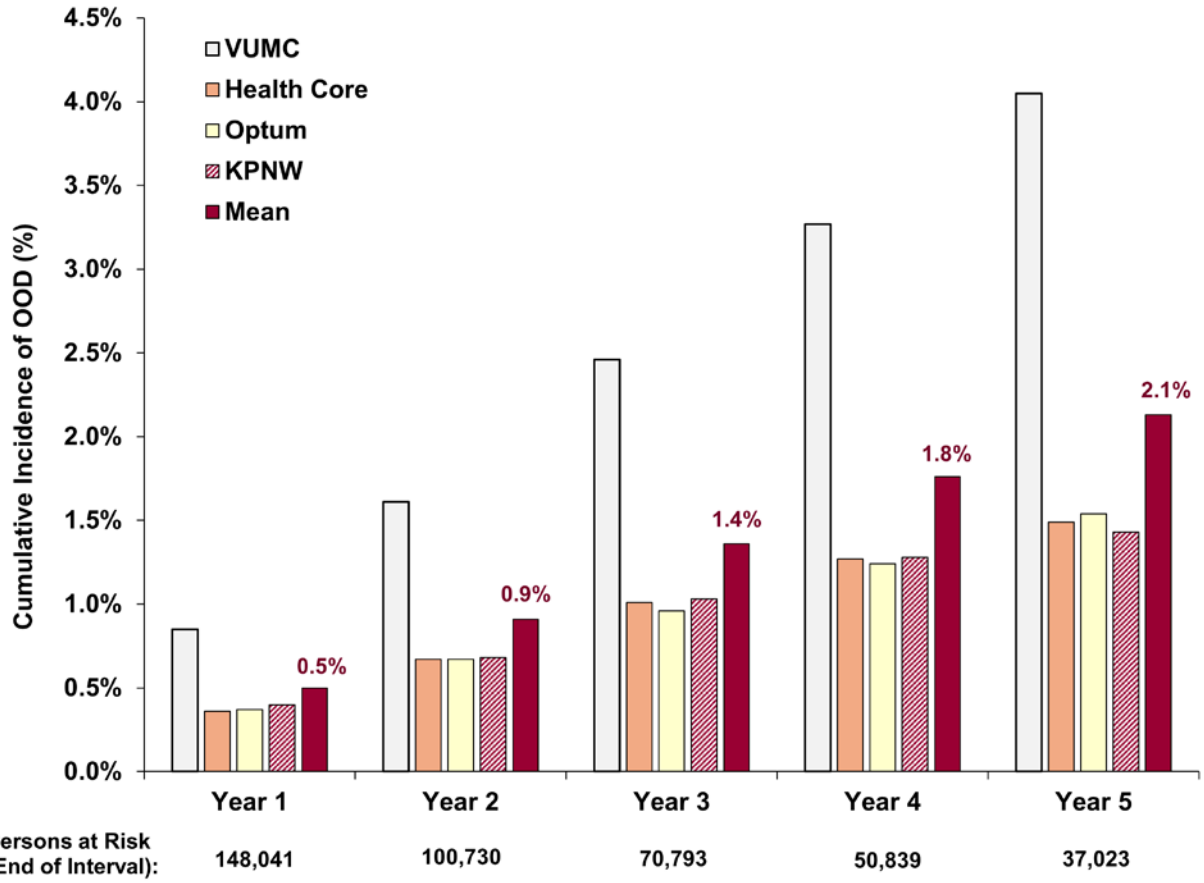
	VUMC	HealthCore	Optum	KPNW	Overall
Cohort entrants	71,932	81,782	54,515	12,020	**220,249**
Person-years (py)	244,191	197,661	87,783	47,599	**577,234**
OOD events	1,978	629	287	140	**3,034**
OOD events, fatal	330	107	57	15	**509**

KPNW = Kaiser Permanente Northwest; OOD = opioid-involved overdose or opioid overdose-related death; py = person-years; VUMC = Vanderbilt University Medical Center

The risk of OOD rose steadily from cohort entry through at least 5 years of follow-up (Figure 16). The first-year average cumulative risk was 0.50%, rising to 2.13% at the end of 5 years, with the rate of increase being slightly higher in the first year than in the subsequent 4 years. The 5-year cumulative risk of OOD was highest in the VUMC data (4.05%). Five-year cumulative risks were similar between the 2 national commercial health insurers (Optum and HealthCore, at 1.54% and 1.49%, respectively) and the non-profit health care organization (KPNW, at 1.43%).

Administrative termination through change of health plans was the most common reason for exit from the study. The number of persons under observation declined with time; of 220,249 persons at cohort entry, 67% remained under observation through 1 year, while 32% remained through 3 years. At 5 years, 17% of the original cohort members remained under observation.

Figure 16: Cumulative Incidence (Risks) of Opioid-Involved Overdose or Opioid Overdose-Related Death (OOD) Through 5 Years – Overall and by Study Site – Study 3033-2



KPNW = Kaiser Permanente Northwest; OOD = opioid-involved overdose or opioid overdose-related death; VUMC = Vanderbilt University Medical Center.

Effect of Baseline Characteristics on Follow-up in the Primary Cohort:

VUMC cohort members, who were exclusively Tennessee Medicaid recipients, and cohort members identified through KPNW, an accountable care organization in the Pacific Northwest, had substantially longer average duration of membership, and therefore time on study, than did members identified through 2 commercial insurance databases (Optum and HealthCore). Cohort members with a prior diagnosis of OUD left their respective insurance plans somewhat more rapidly than those without the diagnosis. No other characteristic consistently predicted time-on-study.

Secondary Analysis for Participants with Uninterrupted Opioid Treatment:

A secondary analysis was performed by restricting follow-up to the period following cohort entry during which there was uninterrupted treatment with a Schedule II opioid. This analysis yielded much shorter follow-up times than for the full analysis of the primary cohort, whether "uninterrupted treatment" was determined accounting for possible drug stockpiling or not. Without accounting for stockpiling through 2 years of follow-up, at which time only 14% of the cohort remained under

continuous treatment, the cumulative risks of OOD were close to those reported for the primary analysis, where there was no requirement for uninterrupted treatment.

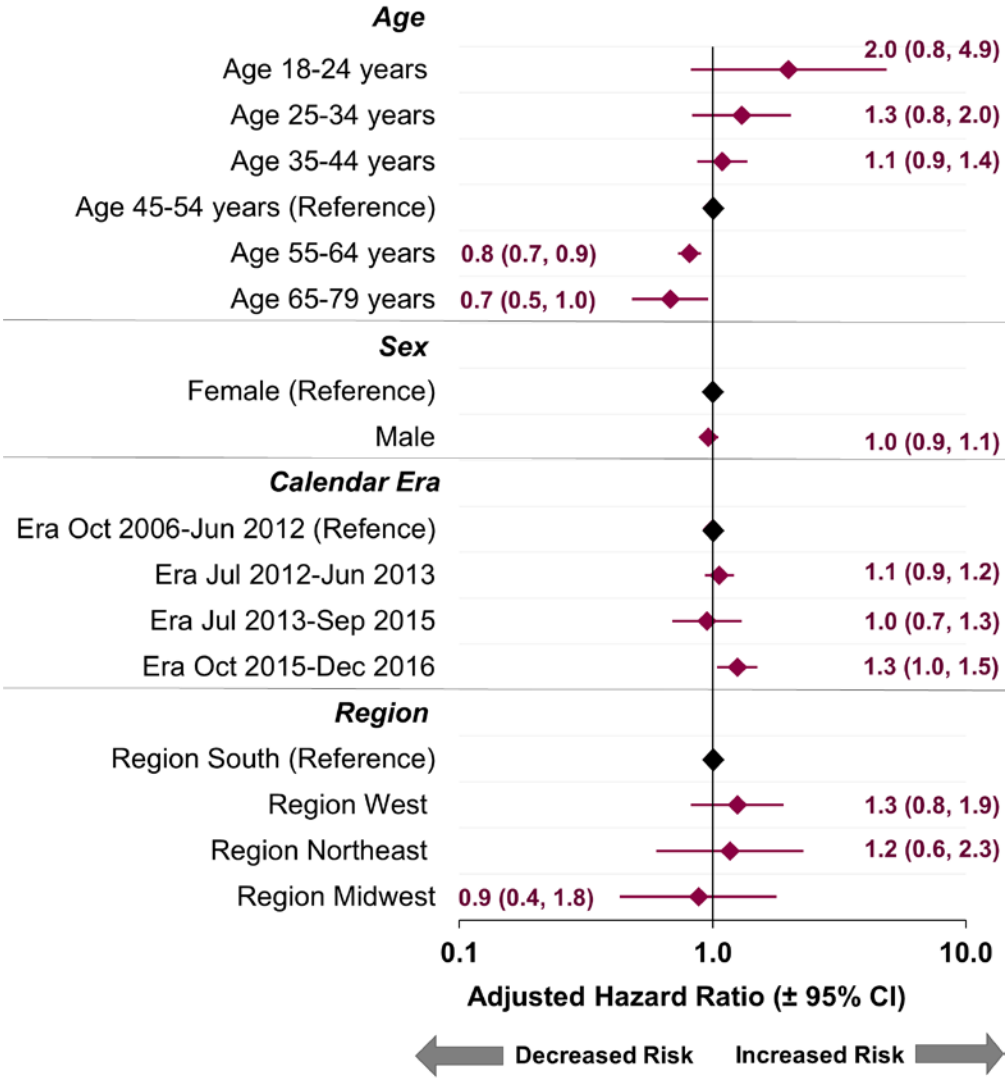
Secondary analyses (a) for a relaxed cohort entry criterion that permitted prior opioid use up to 30 days before the beginning of the Qualification Period, and (b) for outcomes not designated as resulting from intentional self-harm are reported under secondary objectives 4 and 5 (Section 5.2.3.2.3 and Section 5.2.3.2.4, below).

5.2.3.1.2. Study 3033-2 – Potential Risk Factors for Opioid-Involved Overdose or Opioid Overdose-Related Death (OOD) (Primary Objective 2)

Meta-analytic summary HRs with the demographic covariates forced into all models are summarized in Figure 17. Age showed a monotonic decrease in risk after adjustment for sex, calendar era, and Census Region. Compared to 45 – 54-year-olds (the most prevalent group), the youngest patients (18 – 24 years) had twice the risk of OOD (HR 1.99; 95% CI: 0.82, 4.87), while the oldest patients (aged 65 – 79 years) had over 30% less risk (HR 0.68; 95% CI: 0.48, 0.96).[b] Men and women had approximately the same risk after adjustment for age, region, and calendar era. After adjustment for other demographic factors, there was little trend in risk over calendar era. Only Optum and HealthCore had data spanning multiple US Census Regions, and these did not point to consistent differences between regions. All these relationships pertain to the studied population only: persons with long-term prescription opioid dispensings whose experience was captured in health insurance systems.

[b] The decline was not the same at every site, being essentially absent in the VUMC (Medicaid) data and present everywhere else.

Figure 17: Meta-Analytic Summary Hazard Ratios (± 95% CI) for Opioid-Involved Overdose or Opioid Overdose-Related Death (OOD) by Demographic Covariate (Adjusted for Age, Sex, Calendar Era and Census Region) – Study 3033-2

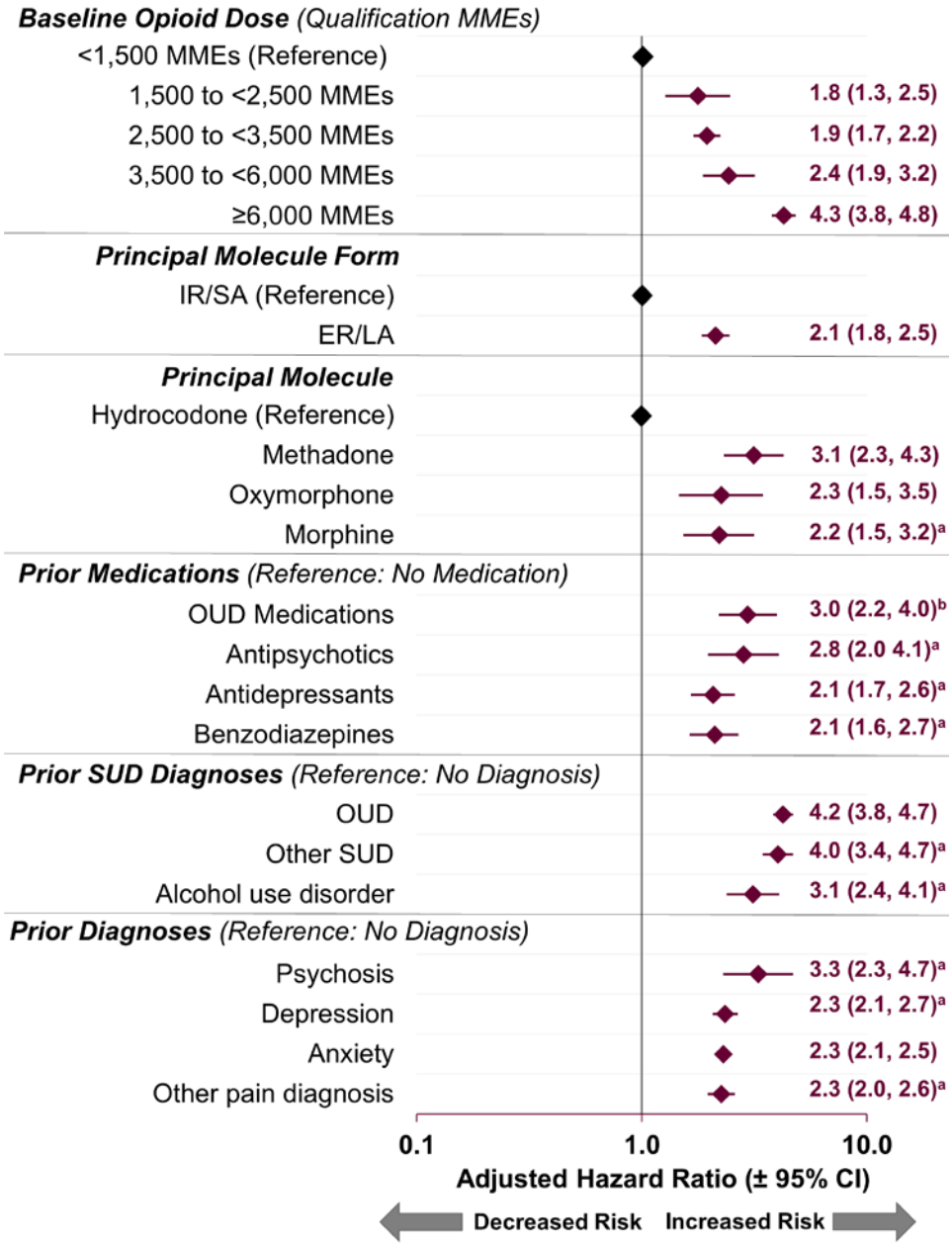


CI = confidence interval; KPNW = Kaiser Permanente Northwest; OOD = opioid-involved overdose or opioid overdose-related death; US = United States; VUMC = Vanderbilt University Medical Center.
Notes: VUMC results pertain entirely to the South US Census Region and KPNW to the West. There are no separate regional hazard ratios comparing other regions to the South estimable from these sites. There were additionally 113 cohort members at HealthCore for which the region was "other/unknown" and among whom there were no events.
Data for percentage of cohort, heterogeneity index (I^2), number of sites, and p-values are provided in Appendix 9.2.1.

Meta-analytic summary HRs for potential risk factors related to principal molecule, principal molecule form, prior diagnoses and medications, and baseline opioid dose (Qualification MMEs) are summarized in Appendix 9.2.1. Characteristics associated with at least double the risk for OOD (HR ≥ 2.0) across all 4 sites after adjustment for demographics (age, sex, calendar era, and US Census Region; Figure 18) included opioid dose dispensed during the Qualification Period, pre-existing OUD, 2 infrequently used principal molecules (methadone, oxymorphone), use of ER/LA as opposed to

IR/SA opioids, and prior diagnosis of anxiety. Prior use of medications for OUD was a strong potential risk factor across the 3 sites where it was assessed. As indicated by heterogeneity indices (I^2) greater than 0.50, further strong risk factors for which there were substantial differences between sites included morphine as a principal molecule, diagnoses of non-opioid SUDs (alcohol and other), "other" pain, psychosis, and depression, together with medications for treatment of the pre-existing psychiatric conditions.

Figure 18: Meta-Analytic Summary Hazard Ratios (± 95% CI) for Opioid-Involved Overdose or Opioid Overdose-Related Death (OOD) by Baseline Opioid Dose (Total Qualification MMEs), and Principal Molecule, Formulation, Prior Diagnoses, and Prior Medications (aHR ≥ 2.0 at all 4 Sites) (Adjusted for Age, Sex, Calendar Era and Census Region) – Study 3033-2



CI = confidence interval; ER/LA = extended release/long-acting; IR/SA = immediate-release/short-acting; MME = morphine milligram equivalents; OOD = opioid-involved overdose or opioid-overdose-related death; OUD = opioid use disorder; SUD = substance use disorder.

a. Higgins and Thompson heterogeneity index (I^2) > 0.50.

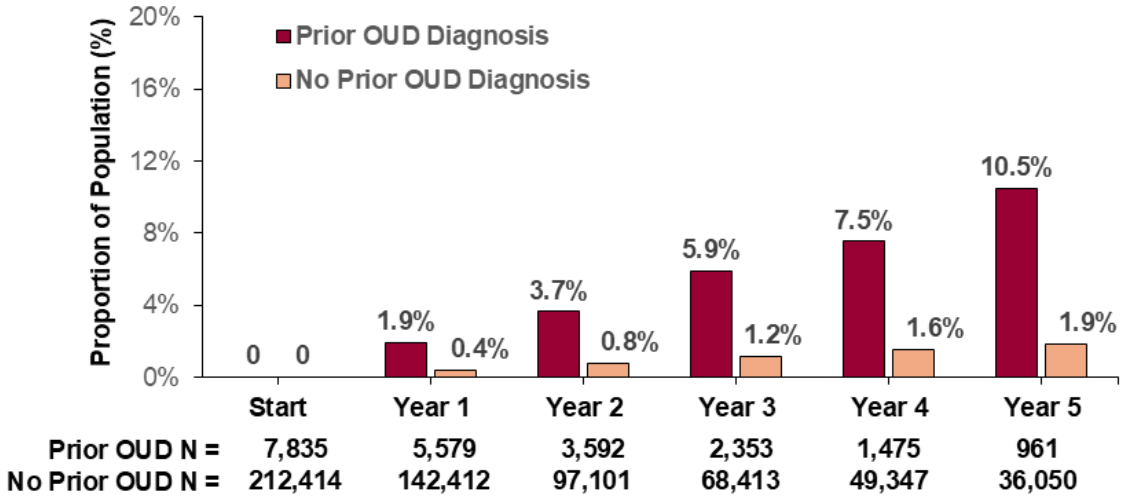
b. Medications for OUD were generally not recorded at Kaiser Permanente Northwest because substance use treatment was contracted outside of their system. The corresponding summary is across the remaining 3 sites.

Baseline opioid dose/Qualification MMEs includes the total MMEs of Schedule II opioids dispensed during the 90-day Qualification Period prior to the Cohort Start Date.

Data for % of cohort, heterogeneity index (I^2), and p-values are provided in Appendix 9.2.1.

As an illustration of the effect of a strong predictor from the previous figure (Figure 18), Figure 19 shows that patients with a baseline diagnosis of OUD experienced a much more rapidly increasing cumulative risk of OOD compared with those without the diagnosis.

Figure 19: Cumulative Risks of Opioid-Involved Overdose or Opioid Overdose-Related Death (OOD) by Prior Opioid Use Disorder Diagnosis – Study 3033-2

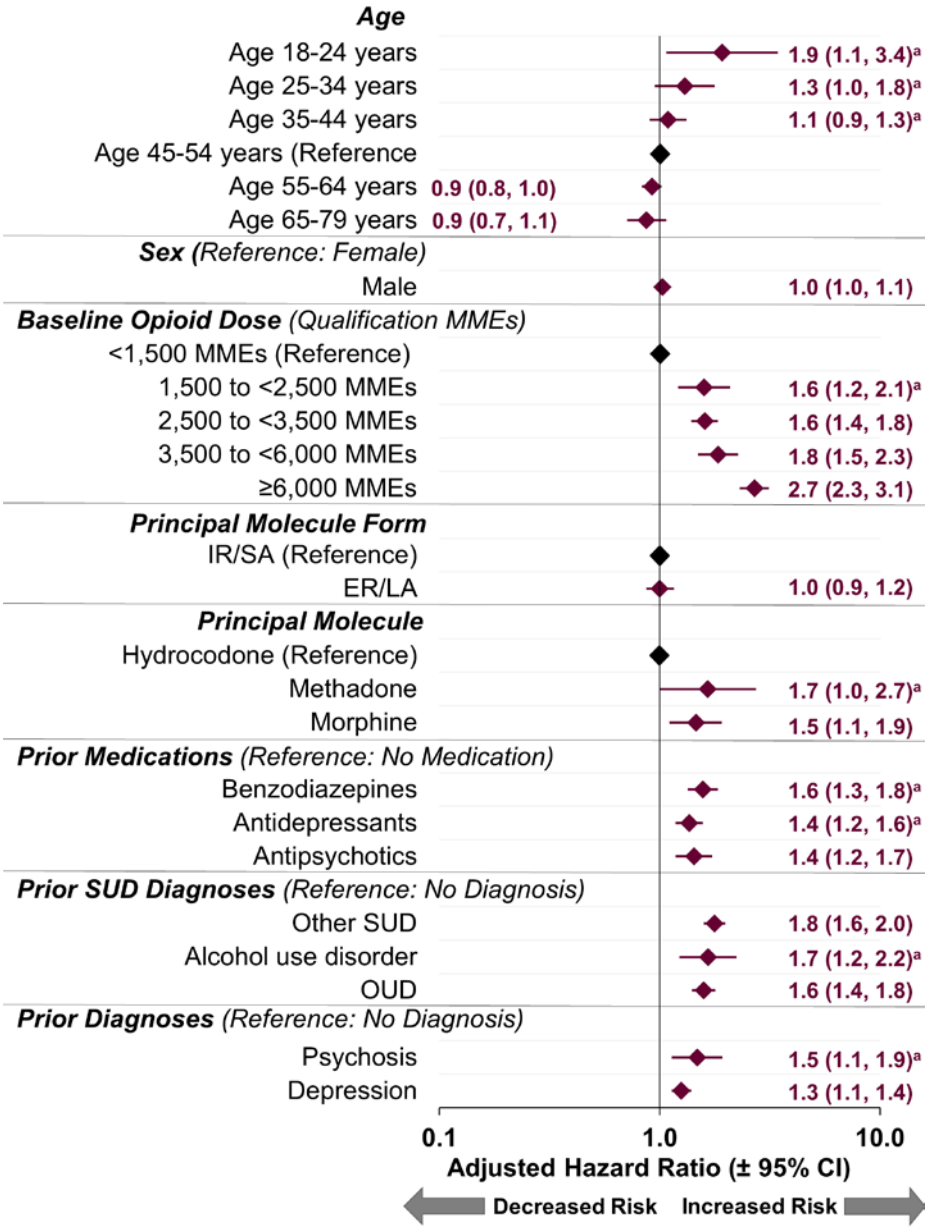


OOD = opioid-involved overdose or opioid overdose-related death; OUD = opioid use disorder.

All risk estimates were substantially reduced when the baseline covariates were adjusted for one another and for baseline (Qualification Period) opioid dose, indicating a corresponding degree of mutual correlation (Figure 20). Even after adjustment for all predictors, the highest baseline opioid dose quintile (≥ 6000 MMEs dispensed in 90 days) was associated with more than a doubling of risk compared to the lowest quintile (fully-adjusted summary HR 2.69; 95% CI: 2.31, 3.13; heterogeneity index = 0.00). The importance of baseline MME as a predictor, to the near exclusion of all other measured factors, suggests that the predictive value of most, if not all, covariates could be attributable to correlations with opioid dose. Use of ER/LA opioids was associated with no added risk of OOD in the fully-adjusted model (summary HR 1.00; 95% CI: 0.87, 1.16; heterogeneity index 0.00).

Because not all sites had enough OOD events to support estimation of regression coefficients for all covariates, only the covariates that were retained after site-specific stepwise regressions are shown in Figure 20. Omission of covariates from the site-specific adjustments occurred when the p-value for the corresponding regression term was greater than 0.1. The exclusion of a covariate from the model for any site amounted to forcing the corresponding nonsignificant site-specific coefficient to the null.

Figure 20: Fully-Adjusted Model (Including Adjustment for Total Qualification Period MMEs): Meta-Analytic Summary Hazard Ratios (± 95% CI) for Opioid-Involved Overdose and Opioid Overdose-Related Death (OOD) – Study 3033-2



CI = confidence interval; ER/LA = extended-release/long-acting; IR/SA = immediate-release/short-acting; OUD = opioid use disorder; MME = morphine milligram equivalents; OOD = opioid-involved overdose and opioid-overdose-related death; SUD = substance use disorder.

[a.] Higgins and Thompson heterogeneity index (I^2) > 0.50.

Because not all sites had a sufficient number of OOD events to support estimation of regression coefficients for all covariates, only the covariates that were retained after local stepwise regressions are shown.

Baseline opioid dose/Qualification MMEs includes the total MMEs of Schedule II opioids dispensed during the 90-day Qualification Period prior to the Cohort Start Date.

The reference category for the principal molecule variables in the meta-analysis was hydrocodone plus, in each site, the molecules that were not statistically distinguishable from hydrocodone at $p < 0.10$ in stepwise regression.

Data for percentage of cohort, heterogeneity index (I^2), number of sites, and p-values are provided in Appendix 9.2.1.

5.2.3.2. Study 3033-2 Secondary Objectives

5.2.3.2.1. Study 3033-2 – Cohort Demographics and Characteristics (Secondary Objectives 1 and 2)

Baseline Demographics and Characteristics (Secondary Objective 1):

Table 7 presents summaries of demographics and baseline characteristics at the Cohort Start Date. At baseline, most cohort members were ≥ 45 years of age, with an approximately even split between males and females. Most of the cohort was resident in the South US Census Region, followed by the West. IR/SA hydrocodone was the most common principal molecule at baseline, followed by IR/SA oxycodone. As in Study 3033-1, psychiatric comorbidities (depression, anxiety, psychosis) and other medication use (antidepressants, benzodiazepines, muscle relaxants) were relatively common. SUD diagnoses prior to cohort entry were present in ~ 5% of cohort members.

Table 7: High-Level Summary of Demographic and Baseline Characteristics of Interest at Cohort Start Date in Study 3033-2

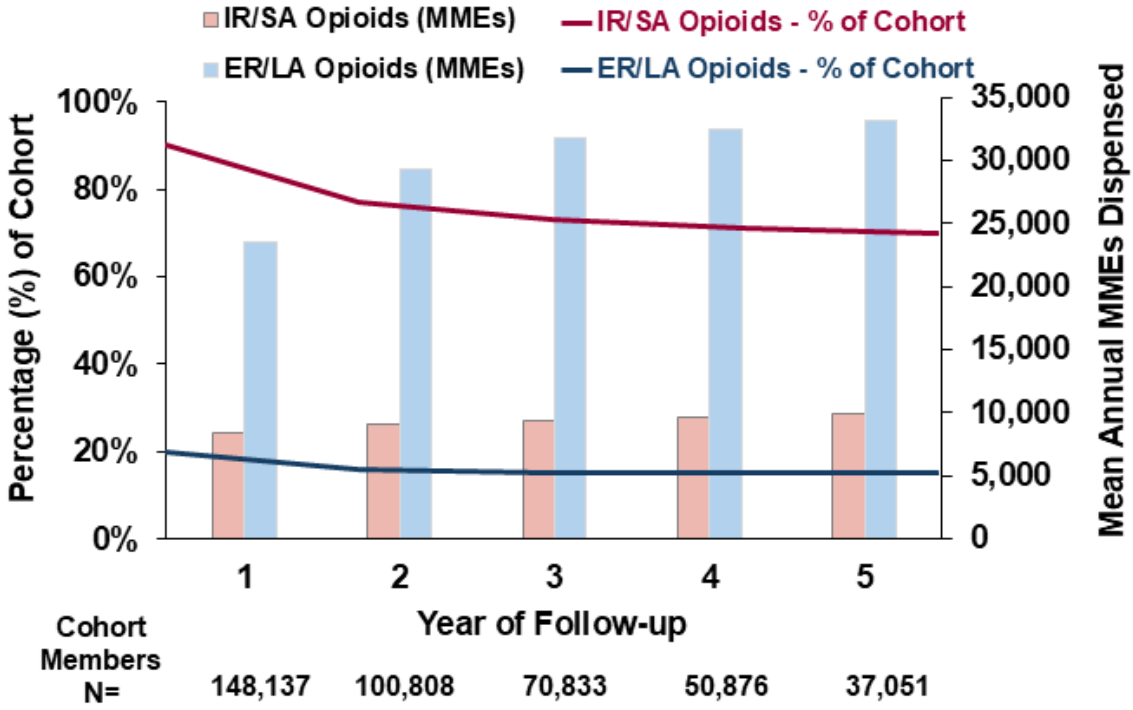
Demographic/Baseline Characteristic	Summary of Data
Age	65.4% ≥ 45 years
Sex (male / female)	48.9% / 51.1 %
US Census region	58.5% South; 18.9% West; 16.4% Midwest; 6.1% Northeast
Era	64.3% Oct 2006 – Jun 2012; 17.3% Jul 2013 – Sep 2015
Principal molecule at start date	58.9% hydrocodone IR/SA 22.4% oxycodone IR/SA 5.1% fentanyl ER/LA 4.4% morphine ER/LA 4.1% oxycodone ER/LA
PM formulation	83.9% IR/SA 15.9% ER/LA
Qualification Period Total MMEs	22% < 1,500 mg 23% 1,500 – < 2,500 mg 16% 2,500 – < 3,500 21% 3,500 – < 6,000 19% ≥ 6,000
Pain diagnoses prior to cohort entry	56.9% back 57.3% limb/extremity/joint 26.1% fractures 9.8% neuropathy 20.8% other
Mental health diagnoses prior to cohort entry	26.5% depression 25.4% anxiety 8.1% psychosis
SUD prior to cohort entry	6.0% non-alcohol, non-opioid 5.0% alcohol 3.6% opioid
Medications used prior to cohort entry	34.1% antidepressants; 31.7% muscle relaxants 31.5% benzodiazepines 20.6% gabapentinoids 5.9% antipsychotics

ER/LA = extended-release / long-acting; IR/SA = immediate-release/short-acting; MME = morphine milligram equivalents; SUD = substance use disorder; United States.
Note: Table displays the most common responses for demographic and baseline characteristics of interest.

Characteristics of the Cohort Over Time (Secondary Objective 2):

A substantial proportion of cohort members who remained with insurance coverage and therefore under observation continued to use Schedule II opioids throughout the follow-up period (Figure 21). In each of Years 2 – 5, at least 70% of the observed cohort received dispensings for IR/SA opioids and ~15% received dispensings for ER/LA opioids, with over 200 days of opioid treatment supplied per year for each of the formulations (210 – 217 days for IR/SA opioids and 206 – 268 days for ER/LA opioids).

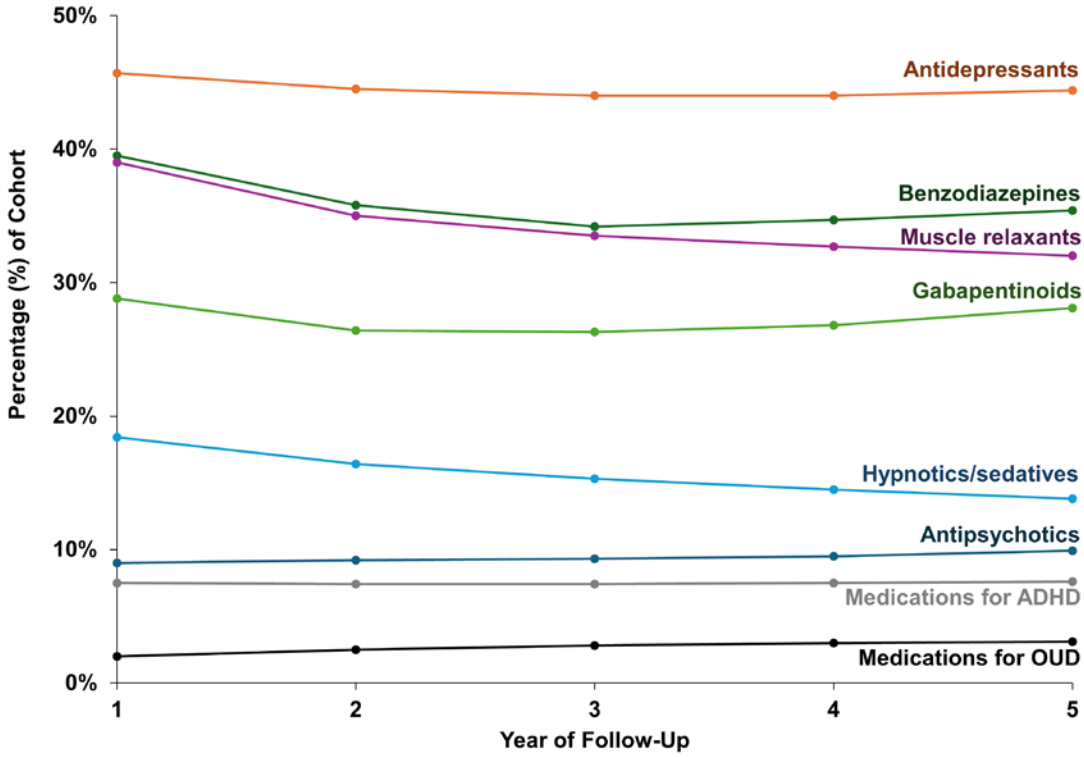
Figure 21: Schedule II Opioid Treatment during 5 Years of Follow-up – Study 3033-2



ER/LA = extended-release/long-acting; IR/SA = immediate-release/short-acting; MME = morphine milligram equivalents.
Note: ER/LA and IR/SA opioids include Schedule II opioids only.
Means are weighted across the sites according to the site-specific numbers of cohort members at the end of each interval.

Dispensings for antidepressants, benzodiazepines, muscle relaxants, and gabapentinoids remained high throughout follow-up (Figure 22).

Figure 22: Non-Opioid Treatment during 5 Years of Follow-up – Study 3033-2



ADHD = attention-deficit/hyperactivity disorder; OUD = opioid use disorder.
Note: All counts are sums. Means are weighted across the sites according to the site-specific numbers of cohort members at the end of each interval.

5.2.3.2.2. Study 3033-2 – Cumulative Risk and Incidence in Risk-Factor-Defined Strata (Secondary Objective 3)

Each of the site-specific and covariate-level-specific cumulative risks resembled the overall cumulative risk figures, within the limitations of small sample size for the smaller populations captured by the stratifications. There was no suggestion that the steady rise in cumulative risk was limited to segments of the population defined by site or covariates.

5.2.3.2.3. Cohort Expanded with Shorter Baseline Opioid Dispensing Period (Secondary Objective 4)

Persons with Schedule II opioid dispensings 183 to 31 days before the beginning of the Qualification Period were excluded from the primary study cohorts. Secondary Objective 4 served as a sensitivity analysis, allowing for the inclusion of persons who had used Schedule II opioids as recently as 30 days before the start of the Qualification Period. The resulting expanded cohort experienced cumulative risks similar to those of the primary cohort. The average cumulative risk of OOD at one year was 0.5%; at 5 years it was 2.2%.

5.2.3.2.4. Evaluation of Intentionality (Secondary Objective 5)

Through 5 years of follow-up, 24.5% of the OOD events were classified as being the consequence of intentional self-harm, according to the identifying ICD codes. Removal of these events proportionally lowered the cumulative risk curves within each of the sites and overall. The average cumulative risk of OOD not classified as intentional at one year was 0.4%, and at 5 years, it was 1.6%.

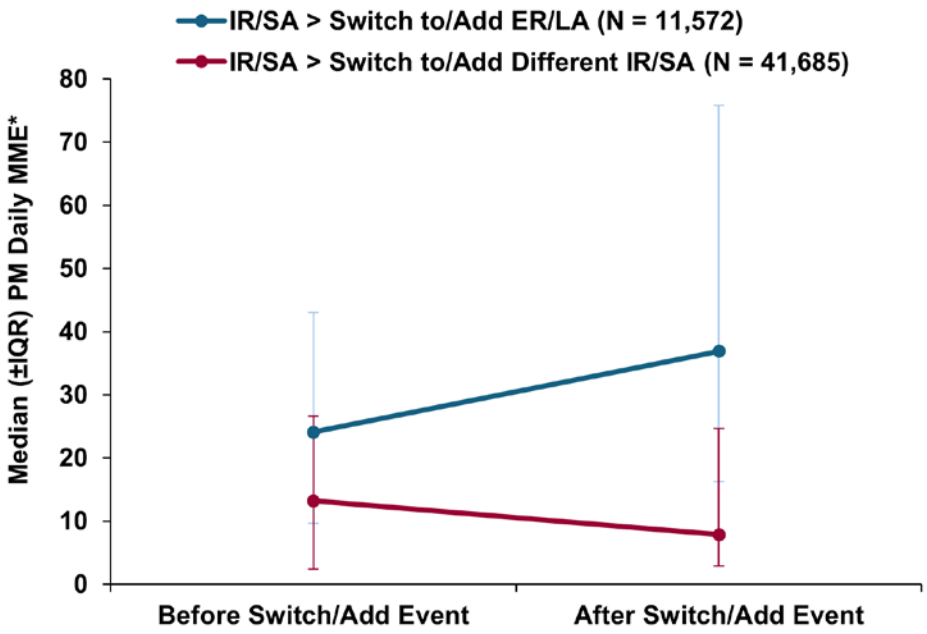
5.2.3.2.5. ER/LA Switch/Add Cohort (Secondary Objective 6)

Overall, 53,257 users of IR/SA opioid formulations entered the Switch/Add Cohort; for 11,572 of these cohort members, prescribers introduced an ER/LA opioid, and for 41,685 of these cohort members, prescribers introduced a new IR/SA opioid therapy.

Opioid dose in the pre-Switch/Add period was a strong predictor of switching to or adding an ER/LA opioid. Other predictors observed across sites were associated with ORs ≤ 2.

As illustrated in Figure 23, cohort members in the ER/LA opioid Switch/Add group had already been receiving higher IR/SA opioid doses before the introduction of the new opioid compared to those in the IR/SA opioid Switch/Add group. Median daily opioid dose increased by ~ 53% over the 90-day post-index date period after a Switch/Add to an ER/LA opioid, while median daily MME decreased by ~ 41% from before to after a Switch/Add event in the IR/SA Switch/Add group.

Figure 23: Summary of Median (IQR) Daily MMEs Before and After Switch/Add Event in the Switch/Add Cohort – Study 3033-2



ER/LA = extended-release/long-acting; IQR = interquartile range; IR/SA = immediate-release/short-acting; MMEs = morphine milligram equivalents.
* Median daily morphine milligram equivalents over 90 days.
IR/SA > Switch to/Add ER/LA included patients who entered the cohort as primarily IR/SA opioid recipients who subsequently switched to or added an ER/LA opioid.
IR/SA > Switch to/Add Different IR/SA included patients who entered the cohort as primarily IR/SA opioid recipients who subsequently switched to or added a different IR/SA opioid product.

Persons who introduced Schedule II ER/LA opioids experienced higher rates of OOD than persons who introduced an IR/SA opioid (either 4 or 6 added events person 1,000 py, depending on the rule for end of follow-up) (Table 8). Rate differences and ratios were higher when evaluated to the end of the Switch/Add treatment than when the observation continued to the Cohort End Date. Following adjustment for daily MME prior to the Switch/Add event and the Qualification Period MMEs, values of the HRs were little changed relative to the incidence rate ratios that were not adjusted for these factors.

Table 8: Summary of Opioid-Involved Overdose and Opioid Overdose-Related Death (OOD) Rates in the Switch/Add Cohort in Study 3033-2

End of Observation	IR/SA to ER/LA	IR/SA to IR/SA	ER/LA vs. IR/SA Estimate (95% CI)
Switch/Add Cohort (N = 53,257)			
No. of members (% of cohort)	11,572 (21.7%)	41,685 (78.3%)	
Cohort End Date			
OOD events	333	812	
py (1000s)	30.3	111.2	
Rate per 1000 py (95% CI)	11.0 (9.9, 12.2)	7.3 (6.8, 7.8)	
		Rate Difference (95% CI):	3.7 per 1000 py (2.4, 5.0)
		Rate Ratio (95% CI):	1.50 (1.32, 1.71)
		Meta-Analysis PHM HR (95% CI):	1.43 (1.09, 1.88)
		Adjusted (Qualification MME)[a] HR (95% CI):	1.38 (1.05, 1.81)
		Adjusted (Daily MME)[b] HR (95% CI):	1.35 (1.02, 1.77)
Discontinuation of Switch/Add Treatment			
OOD	62	77	
py (1000s)	4.7	10.4	
Rate per 1000 py (95% CI)	13.2 (10.3, 17.0)	7.4 (5.9, 9.3)	
		Rate Difference (95% CI):	5.8 per 1000 py (2.1, 9.5)
		Rate Ratio (95% CI):	1.78 (1.28, 2.49)
		Meta-Analysis PHM HR (95% CI):	1.64 (1.15, 2.34)
		Adjusted (Qualification MME)[a] HR (95% CI):	1.69 (1.17, 2.44)
		Adjusted (Daily MME)[b] HR (95% CI):	1.59 (1.10, 2.30)

CI = confidence interval; ER/LA = extended-release/long-acting; HR = hazard ratio; IR/SA = immediate-release/short-acting; MME = morphine milligram equivalents; OOD = opioid-involved overdose or opioid overdose-related death; PHM = proportional hazards model; py = person-years.
Note: The meta-analyzed HRs from the site-specific models were close to the crude rate ratios, indicating little net confounding.

5.2.3.2.6. Partial Assessment of Validity of ICD-10 Codes (Secondary Objective 7)

Three sites (VUMC, HealthCore, and KPNW) performed chart audits of 428 records for OOD events that had occurred following the US nationwide change from ICD-9 to ICD10 coding for health insurance claims (October 1, 2015). The purpose of the audits was to extend the validation activities originally conducted using ICD-9 codes in Study 3033-6. The medical record showed "definite" documentation of an OOD event in 343 cases occurring during the period of utilization of ICD-10. The positive predictive value (PPV) was therefore 80.1% (95% CI: 76.1, 83.6). Another 30 of the 428 records had documentation that was "suggestive" of OOD; inclusion of these as true OOD events increased the PPV to 87.1% (95% CI: 83.6, 90.0).

5.2.4. Study 3033-2 Discussion and Interpretation

Study 3033-2 presents the multiyear progression of risk of OOD in large cohorts of new long-term users of Schedule II opioids. At baseline, cohort members were primarily middle-aged (over half being between the ages of 45 and 64 years). Owing to the distribution of service areas of the participating sites, more than half of patients resided in the South Census Region, and for more than half again, IR/SA hydrocodone was the molecule contributing the greatest MMEs during the 90-day Qualification Period before the start of follow-up. In more than half of the remaining members, oxycodone was the principal contributor to baseline MME. As in Study 3033-1, comorbidities and other medication use were relatively common. A small minority of the cohort had SUD diagnoses prior to cohort entry, most of these patients being found in the VUMC (Medicaid) population.

The risk of OOD was 13.8 events per 1,000 persons (or 1.3%), with an incidence rate of 5.3 OOD events per 1,000 py (95% CI: 5.1, 5.5). Overall, 16.8% of OOD events were fatal. The risk of OOD was ~ 0.5% in the first year of follow-up, rising to just over 2% through 5 years. The risk of OOD was highest in the site that used only Medicaid data (VUMC), lower in the sites using national commercial insurance data (Optum and HealthCore), and lowest in the non-profit health care system (KPNW). VUMC patients also had higher prevalence of mental health diagnoses, including SUDs, at baseline. These factors, along with socioeconomic factors, may have contributed to the higher risk of OOD in this population.

Through 5 years of follow-up, 75.5% of the overall OOD events were not classified as intentional self-harm using the ICD-9 and ICD-10 codes. Removal of the events classed as intentional proportionally lowered the average cumulative risk of OOD to 0.4% at 1 year and 1.6% at 5 years.

Dispensings for Schedule II opioids remained high through 5 years, despite at least a year's non-use prior to the Qualification Period having been a cohort entry criterion. Dispensings of Schedule II opioids occurred in over 70% of patients during each year of follow-up; dispensings for antidepressants, benzodiazepines, muscle relaxants, and gabapentinoids also continued (ranging between 26% and 46%). Thus, although the opioid dispensings that defined and preceded cohort entry was far removed from the subsequent OOD events, the exposure was sufficient to mark the beginning of long-term dispensings for both opioids and other agents that are generally discouraged as co-medications with opioids. The repeated ongoing dispensings for a variety of agents complements the findings of PMR Study 3033-1, where new extended use of opioids (similar to the Qualification Period usage in 3033-2) was followed within a year by nearly a quarter of patients reporting signs of prescription opioid misuse, along with smaller proportions reporting abuse or OUD.

The strongest baseline risk factor for long-term risk in the demographically-adjusted models was the quantity of opioids dispensed during the Qualification Period, with the highest quintile (≥ 6000 MMEs or more dispensed in 90 days) having over 4 times the risk of the lowest dosing quintile (< 1500 MMEs). A variety of baseline opioid use measures (principal molecules methadone, oxymorphone, and morphine; ER/LA formulation) and baseline conditions that could be expected to continue through follow-up (e.g., diagnosis of OUD, diagnoses of anxiety, psychosis or depression, non-opioid SUDs, medications used for these conditions) were noted after control for demographic covariates, but all effect estimates were dramatically reduced with control for baseline MME. This result is notable because examining the use of ER/LA formulations was a major impetus for the PMR 3033 studies; the HR for baseline ER/LA versus IR/SA use was nil (HR = 1.0) after control for baseline opioid dose.

The Switch/Add sub-study (secondary objective 6) entailed a further examination of risks associated with ER/LA and IR/SA opioids by forming cohorts of persons whose dispensing patterns suggested a change of treatment regimen from an apparently stable use of an IR/SA opioids. When an opioid that had not been previously used was dispensed, the recipient entered the Switch/Add cohort as a new recipient of an ER/LA or IR/SA product. Subsequent occurrence of OOD was monitored and risks were calculated with adjustment for the same covariates as had been defined for the primary cohort, but updated to the 90 days before the Switch/Add event. In comparison to switching to or adding on a new IR/SA opioid, the switch to or adding on of an ER/LA opioid was associated with an increased risk of OOD of 4 to 6 events per 1,000 person-years, depending on the choice of follow-up period, compared to those who switched to new IR/SA opioids. The new ER/LA opioid users received higher doses of opioid after the Switch/Add event than did the new IR/SA patients, raising the possibility that the risk may have been attributable in part to the new treatment regimens' inclusion of an increase in dose along with a change in formulation.

Study 3033-2 benefited from large size, wide geographic variety in practice settings, and independent conduct within 4 separate data sources and research sites. The investigators all had extensive prior experience in FDA-required and -sponsored safety studies. Because data sources were administrative, it was possible to identify risk factor variables that were present before follow-up began, independently of study outcomes. Drug dispensings that were reimbursed by insurance plans at each of the sites had been recorded with details of date, quantity, and specific product. The study had no access to data on the use of self-paid or illicitly obtained opioid products or other drugs. Although the assignment of a diagnosis in routine medical care is not standardized, the validation studies carried out internally and in PMR Study 3033-6 indicate that the outcome definition was of adequate sensitivity and specificity to support this descriptive study.

5.2.4.1. Relationship of Study 3033-2 Results to Previous Findings

Rates of OOD in long-term opioid users identified in Study 3033-2 were within the ranges previously reported in the literature. For example, using an interrupted time series design in patients enrolled in a group health care organization in Washington State, Von Korff et al. found overall rates of OOD in chronic users of opioids to be 4.9 per 1,000 py for the period between 2006 and 2014 (Von Korff et al., 2019). Several other studies with entry criteria that differed from those of Study 3033-2 have provided OOD incidence rate estimates that bookend the values obtained in this study (Dunn et al., 2010; FDA Briefing Document, 2020; Miller et al., 2015). Dunn et al. (2010) reported an overall OOD incidence rate of 1.5 per 1,000 py, and the opioid-involved overdose mortality rate was 0.2 per 1,000 py; however, this cohort appears to have received substantially lower doses of Schedule II opioids during follow-up than Study 3033-2 cohort members. In Veterans who had received at least a single

dispensing of any opioid, the OOD rate with ER/LA formulations was 1.6 per 1,000 py (Miller et al., 2015). Purdue PMR Study 3051-4 found rates of OOD events of 12.5 per 1,000 py in commercial databases and 30.5 per 1,000 py in Medicaid (Beachler et al., 2022; FDA Briefing Document, 2020). However, PMR Study 3051-4 was restricted to current use, and the OOD numerators were not restricted to first events. Considering these studies together, it appears that the more intense the opioid therapy required for cohort entry, the higher the measured risk of OOD.

In a recent meta-analysis of 28 observational studies, Wang found a pooled risk of nonfatal opioid overdose of 3.2 per 1,000 persons (95% CI: 2.0, 4.) and a risk of fatal overdose of 1.3 per 1,000 persons (95% CI: 0.6, 2.3) after prescription for chronic pain (Wang et al., 2023). The authors did not specify a follow-up interval; therefore, observing more than a general similarity to the finding of 0.5% average risk (5 per 1,000 persons) of OOD in the first year of follow-up in Study 3033-2 becomes difficult.

Potential risk factors identified in the Wang et al. review (Wang et al., 2023) were consistent with those observed in Study 3033-2. In this study, "*moderate to high certainty evidence supported large relative associations with history of overdose (OR 5.85; 95% CI: 3.78, 9.04), higher opioid dose (OR 2.57; 95% CI: 2.08, 3.18 per 90 mg increment), prescription of fentanyl (OR 2.80; 95% CI: 2.30, 3.41), current SUD (OR 2.62 95% CI 2.09, 3.27), any mental health diagnosis (OR 2.12; 95% CI:1.73, 2.61), depression (OR 2.22; 95% CI: 1.57, 3.14), bipolar disorder (OR 2.07; 95% CI: 1.77, 2.41) or pancreatitis (OR 2.00; 95% CI: 1.52, 2.64).*" Wang and colleagues also noted that use of multiple dispensing pharmacies and prescribers carried elevated risks, in accordance with PMR Studies 3033-8, 3033-9, and 3033-10.

6. SUMMARY, DISCUSSION, AND IMPLICATIONS

6.1. Summary and Discussion of Observational Studies 3033-1 and 3033-2

To date, OPC has completed all 10 of the PMR 3033 series of observational studies; 7 studies have been determined by FDA to have fulfilled PMR requirements, while 3 studies (3033-1, 3033-2, and 3033-6) have been submitted and are under FDA review for PMR fulfillment. Collectively, these studies were conducted to develop and validate measures for, and to assess the incidence of and potential risk factors for, prescription opioid misuse, prescription opioid abuse, addiction, overdose, and death among patients prescribed Schedule II opioid products. Results of the key observational studies, Study 3033-1 and Study 3033-2, were broadly consistent with those in the published literature.

6.1.1. Summary of Study 3033-1 (Misuse, Abuse, and Addiction Outcomes)

Study 3033-1 included large US population–based sub-studies to estimate the cumulative incidence (prospective study) and prevalence (cross-sectional study) of misuse of prescription opioids, abuse of prescription opioids, and addiction (assessed as OUD). Both sub-studies also included an evaluation of potential risk factors for the outcomes. The studies used robust measures of disease, derived from diagnostic interviews and validated self-reported questionnaires, among patients prescribed long-term opioid analgesic therapy for chronic pain. These studies indicated that problematic opioid use exists among long-term users of prescription opioids, and that this use is predominantly comprised of prescription opioid misuse.

From a very large panel of evaluated potential risk factors, those associated with the strongest increases in risk for prescription opioid misuse, prescription opioid abuse, or OUD across cohorts and outcome measures were primarily related to having pre-existing SUDs or other problematic use behaviors. Higher income, being male, Black, or Hispanic, and predominant use of hydromorphone increased the risk associated with several outcomes or cohorts. In the prospective study, prescription opioid misuse among ER/LA Initiators and prescription opioid abuse among LtOT Initiators were significantly associated with use of higher daily opioid doses (≥ 120 MMEs and 90 – 119 MMEs [vs. < 50 MMEs], respectively).

Older age, being obese, exposure to ADFs, and having more severe comorbidity were associated with decreased risk for several outcomes or cohorts, while other potential risk factors were important for individual outcomes or in specific cohorts.

Overall, many of the potential risk factors identified in Study 3033-1 were consistent with those previously reported in the literature. These factors should be considered when weighing the benefits and risks of treating chronic non-cancer pain with long-term opioid therapy, and when considering which patients may warrant closer follow-up and monitoring.

6.1.2. Summary of Study 3033-2 (Overdose and Death Outcomes)

Study 3033-2 presents the multiyear progression of risk of OOD in large cohorts of new long-term users of Schedule II opioids from 2006 to 2017. Cohort members were identified in the files of commercial and non-profit insurers, and from one Medicaid program. Study 3033-2 used consistent methodology across diverse populations, with a follow-up period of up to 5 years.

Cohort members remained under follow-up for as long as they retained insurance coverage, without a requirement for continued opioid use. Nonetheless, continued use of opioids, other analgesics, antidepressants, and benzodiazepines was a prominent feature of the cohorts throughout, as were recurring medical claims associated with painful conditions.

The risk of OOD was ~ 0.5% in the first year of follow-up, rising steadily to a cumulative risk just over 2% after 5 years. The risk of OOD was highest in the site that used only Medicaid data, lower in the sites using national commercial insurance data, and lowest in the non-profit health care system. Removal of OOD events classified as stemming from intentional self-harm (approximately one-quarter of the total) resulted in correspondingly lower risk estimates throughout (0.4% at Year 1 and 1.6% at Year 5).

The strongest baseline potential risk factor was the receipt of a high dose of opioids during the Qualification Period. The HR associated with the highest dose (≥ 6000 MMEs over 90 days) was more than 4 times higher than that associated with Qualification Periods having the lowest quintile of dose (< 1,500 MMEs). Other potential risk factors that were observed after adjustment for demographics included insurance claims diagnoses of pre-existing SUDs and various psychiatric disorders (and dispensing of medications to treat them). Principal molecules morphine, methadone and oxymorphone (all relatively infrequently used in cohort members), and opioid formulation (ER/LA) were also found to be potential risk factors. That baseline MME was the driving factor for other observed associations with OOD is suggested by the reduction of the corresponding covariate estimates in analyses that adjusted for baseline opioid dose.

When ER/LA opioids rather than IR/SA opioids were added to a previously stable dispensing pattern for IR/SA opioids in persons who qualified as long-term users, an increase in prescribed opioid doses accompanied a switch to or adding on of ER/LA opioids, while a decrease in prescribed opioid doses was observed in those who switched to or added on another IR/SA opioid. Switch/Add to an ER/LA opioid was associated with an increase of 4 to 6 events per 1,000 py in the rate of OOD, corresponding to HRs in the order of 1.4 to 1.7.

6.2. Observational Studies 3033-1 and 3033-2 – Strengths and Limitations

Summaries of strengths and limitations of observational studies 3033-1 and 3033-2 are provided in Table 9 and Table 10, respectively.

Table 9: Summary of Key Strengths and Limitations of Observational Study 3033-1

Study 3033-1: **A Prospective Investigation of the Risks of Opioid Misuse, Abuse, and Addiction Among Patients Treated with Opioids for the Treatment of Chronic Pain**	
Strengths	
Geographically-diverse participants receiving care in integrated delivery systems, network/fee-for-service models, and VA. Included ***underserved populations*** All sites were ***well established*** and had: • *Extensive and complete data systems* • Ability to identify opioid use in a *timely manner* using EHRs or claims data • *Ability to contact* enrollees for interviews, surveys, and biospecimen collection • *Ability to link* interview/questionnaire data to current and past EHR and claims data. ***Validated instruments*** and ***well-established assessment and analytic methods*** used to ensure robust findings. ***Breadth and depth of data:*** evaluated a large number of potentially important risk factors for numerous adverse outcomes of long-term opioid use. ***Prospective*** evaluation of outcomes over 12 months, with assessments every 3 months (prospective study)	
Limitation	**Discussion (Including Mitigation Efforts, where Applicable)**
Residual confounding: Combining rich EHR and claims data with survey data provides the most complete information possible, but residual confounding is possible in any observational study.	Used rigorous methods for accurate and complete data collection, adjusted for confounders, and performed secondary sensitivity analyses.
Exposure misclassification: Exposure misclassification would have been possible if participants received medication orders or dispensings at outside facilities where no claim was adjudicated (e.g., use of cash, dispensings from hospitals).	Possibility was expected to be rare – sites achieved near complete data capture on prescription medication use and are considered among the best systems for data capture available.
Outcome misclassification: Lack of a gold standard assessment may have led to outcome misclassification. POMAQ scoring algorithm was not finalized prior to the start of data collection; earlier study participants administered 2 items (assessing concurrent opioid use with other prescribed or illicit drugs) that were	Use of validated questionnaires (POMAQ/PRISM-5-OP) developed specifically for this study Drug testing would not have helped assess misuse, abuse, or addiction.

later found to be difficult to score. The items were scored whenever possible, but the situation may have led to outcome misclassification. The POMAQ and PRISM-5-OP instruments were developed separately and measured different constructs; some participants who met criteria for OUD on PRISM-5-OP did not meet criteria for prescription opioid misuse or abuse on POMAQ. Not feasible to conduct drug testing of subjects.	
Recall bias: Potential recall bias of outcomes and covariates due to retrospective nature of data collection	Questionnaires were validated, and many questions were asked about present-day or recent past to minimize potential recall bias.
Social desirability bias: Underreporting due to social desirability	Certificate of confidentiality obtained, and participants were assured confidentiality of responses during consent and data collection.
Generalizability: Possibility that the sample is not generalizable to other settings, populations, and different opioid users, including individuals obtaining opioids illicitly.	Selection of sites with variability in geographic location, insurance coverage and HMO structures, and populations served, including underserved populations. Inclusion of 2 cohorts with different characteristics (ER/LA and LtOT Initiators) Collecting extensive data in this study on a probability-based sample of the US population not feasible. Study results most generalizable to individuals prescribed Schedule II opioids for treatment of chronic pain in routine care.
Selection bias: Any study that recruits individuals for primary data collection vulnerable to selection bias induced by non-response or partial study completion.	Very few differences in patient characteristics observed between completers and non-completers Incidence weighted to the demographics of the targeted population similar to the unweighted incidence
Low statistical power to detect significant differences across small subgroups for risk factors	Not possible to power for every subgroup. Further, descriptive analyses are important and contribute substantially to knowledge base and areas for future research.
Cross-sectional study: Participants at some of sites with only medication orders (no dispensing data) were enrolled on basis of opioid prescriptions later determined to be nonqualifying	Small number of participants, which are not expected to substantially impact on the study results and conclusions.

Cross-sectional study: Majority of population predominantly using ER/LA opioid formulations; over 50% using ≥ 90 mg MMEs/day; 18% using an ADF; morphine/oxycodone most common opioids	Recruitment strategy was designed to achieve an informative and diverse sample.

ADF = abuse-deterrent; EHR = electronic health records; ER/LA = extended-release/long-acting; HMO = health maintenance organization; ICD = International Classification of Diseases; MMEs = morphine milligram equivalents; POMAQ = Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-OP = Psychiatric Research Interview for Substance and Mental Disorders, DSM-5 opioid version; VA = Veteran's Affairs.

Table 10: Summary of Key Strengths and Limitations of Observational Study 3033-2

Study 3033-2: **Incidence and Predictors of Opioid Overdose and Death among Users of Opioid Analgesics as Measured by Diagnoses and Death Records**	
Strengths	
Participating sites represent a ***range of US health care settings***, drawing data from Medicaid, commercial insurers, or non-profit care organizations alone ***Large cohort study*** permitted a direct and precise estimation of rates of rare events such as OOD, including important subgroups. ***Use of consistent methodology*** across diverse populations ***Follow-up over several years***. Use of ***validated algorithms*** to determine OOD based on both a prior validation study and an internal validation exercise.	
Limitation	**Discussion (Including Mitigation Efforts, where Applicable)**
Treatments were not given at random.	Correlates of treatment characteristics and of risk were identified as covariates and controlled for.
Exposure measurement based on recorded dispensing of opioids and other medications in insurance plans; actual opioid use not observed.	Repeated dispensings were required for study qualification; subsequent dispensings (or their absence) did not enter into the analysis of predictors.
Did not account for opioids obtained legally but paid for in cash, legal products obtained illicitly, illicit opioids, or drugs of abuse.	OOD outcome was not limited to OOD due to prescription opioids and will have included events associated with illicitly obtained opioids or those paid for in cash.
Medical characteristics inferred from diagnoses accompanying medical services on insurance claims or EHR file and billing diagnoses may not correspond to true medical conditions.	Study outcome (OOD) was validated. The covariates likely represent a combination of actual medical conditions and caregiver assessment of which data needed to be recorded.
US health care systems switched from ICD-9-CM to ICD-10-CM during the study. ICD-10-CM uses a revised conceptual structure and thousands of new disease categories.	The aspects of the OOD definition that had been derived and validated in ICD-9 were adapted to ICD-10 and validated in charts from the participating sites.

ICD = International Classification of Diseases; OOD = opioid-involved overdose and opioid overdose-related death; US = United States; VA = Veteran's Affairs.

6.3. Changing Landscape of Medical and Non-Medical Opioid Use

There have been many changes in clinical practice associated with the diagnosis and management of chronic pain and the use of ER/LA opioids since the initial 2065 series of PMRs was issued more than a decade ago. These changes have occurred parallel to the development, data collection, and completion of the PMR 3033 series of observational studies.

Changes in pain management practice largely relate to the release of guidelines, most importantly, the CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016 (Dowell et al., 2016). The recommendations advised that ER/LA opioids should not be used as the initial treatment for pain and should be reserved only for severe, continuous pain. Secondly, the recommendations stated that clinicians should carefully assess individual benefits and risks when prescribing opioid doses ≥ 50 MMEs per day and should generally avoid or carefully justify increasing doses to ≥ 90 MMEs per day. In 2017, the VA/Department of Defense (DVA/DoD, 2017) issued updated guidelines on the use of opioid therapy, including a recommendation to avoid long-term opioid use entirely, with a preference for the use of a non-pharmacological over pharmacological approach. Other federal agencies, such as the Bureau of Prisons and the Indian Health Service, have since implemented similar policies and guidelines.

According to a report submitted to congress by the Department of Health and Human Services (HHS), as of April 2020, 40 states had passed laws that address the prescribing of opioid analgesic medications (DHHS). State-specific legislation, medical and pharmacy boards, Medicaid programs, department of workforce services, and worker's compensation programs adopted policies, guidelines, and regulations that place limits on prescribing opioid analgesic medications and/or require monitoring of opioid prescriptions. Many insurance companies and managed healthcare organizations (including some of those who participated in Study 3033-1) have also implemented policies related to limitations on opioid analgesic prescriptions. These practices have led to a general downward trend in total daily doses of opioids used, use of ER/LA opioid analgesics, and use of high-dose opioids. This trend began even before the release of the CDC guidelines in 2016, and the use of ER/LA opioid analgesics for chronic pain continues to decline year-over-year. In recent years ≥ 90% of opioid prescriptions have been for IR/SA opioids (Schieber et al., 2019; IQVIA® data).

The introduction of guidelines, changes in state laws and medical boards, institutional rules, and payor coverage, have resulted in millions of patients losing partial or full access to the opioids on which they were stable, despite numerous studies demonstrating the harms associated with these involuntary dose reductions or discontinuations. In many cases, patients were discontinued without tapering or with too-rapid tapering (e.g., Mark & Parish, 2019; Nataraj et al., 2022). Several studies have found that patients may be at higher risk of overdose events following tapering or discontinuation of their stable doses of opioid therapy. For example, one study found that post-opioid tapering periods were associated with an adjusted incidence rate of 9.3 overdose events per 100 py compared with 5.5 events per 100 py in non-tapered periods (adjusted incidence rate difference of 1.68 [95% CI: 1.53, 1.85]) (Agnoli et al., 2021). In a case-control study among patients prescribed long-term opioid analgesic therapy, where 228 case patients with incident opioid overdose were matched to 3,547 controls, large variations in dose (SD > 27.2 MME) were associated with a significantly increased risk of overdose compared with more stable doses (matched OR 3.32), independent of opioid dose (Glanz et al., 2019). Effects on

overdose and mortality may be greatest during rapid tapering or abrupt discontinuation. Compared to reductions of 1% to < 15%, dose reductions of 30% to < 100% were associated with higher odds of ED visits, opioid overdose, and all-cause mortality (Metz et al., 2024). In a cohort study in Washington state, discontinuation of chronic opioid therapy was associated with an HR for death of 1.35 (95% CI: 0.92, 1.98) and for overdose death of 2.94 (95% CI: 1.01, 8.61), after adjusting for age and race (James et al., 2019). Oliva et al (2020) examined 887 deaths from overdose or suicide among patients on long-term opioid analgesic therapy and found that stopping treatment was associated with an increased risk of death from overdose or suicide regardless of the length of treatment, with HRs increasing based on the duration of therapy (1.67 for ≤ 30 days to 6.77 for > 400 days). In a study of 194,839 adolescents and adults who initiated opioid prescriptions from 2010 to 2018 and subsequently received long-term opioid analgesic therapy, there were 17,582 acute substance-related morbidity events (claims for ED visits, inpatient hospitalizations, and ambulance transportation with SUD or overdose diagnoses) observed over the follow-up period (median of 965 days). Relative to initial treatment, risk was greater during subsequent periods of daily opioid use > 60 – 120 and > 120 MME; however, risk was also greater during days 1 to 30 after discontinuations than during initial treatment (Quinn et al., 2022).

Other studies have found an increased risk of using illicit or non-prescribed opioids after discontinuation of long-term opioid analgesic therapy. A case control study among 22,962 patients prescribed opioid therapy found that the odds of opioid discontinuation were approximately twice as high in case patients (i.e., patients using heroin; n = 74) than in control patients (those not using heroin; n = 1,045) (Binswanger et al., 2020). Another study found that participants who were discontinued from prescribed opioids were more likely to use heroin and non-prescribed opioid pain relievers more frequently in subsequent quarters compared to participants with unchanged opioid prescriptions (Coffin et al., 2020).

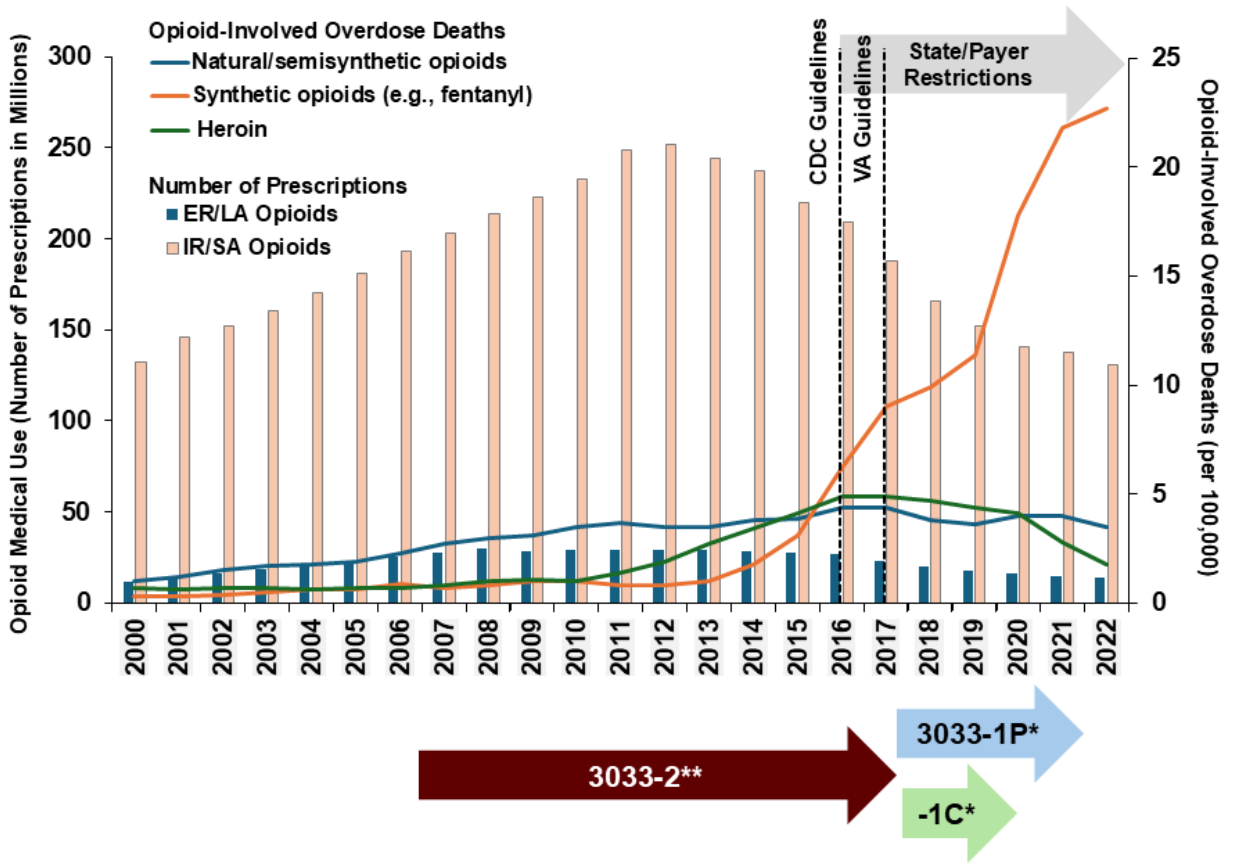
In 2022, CDC released an update to its guidelines, CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022, at least partly due to concerns over the misapplication of the initial 2016 guidelines (Dowell et al., 2022). The CDC's updated 2022 guidelines include the preference for non-pharmacologic and non-opioid pharmacologic therapy for chronic pain as appropriate for the specific patient and the use of opioid therapy only if the benefits are expected to outweigh the risks to the patient. Further, when initiating opioid therapy for acute, subacute, or chronic pain, clinicians are advised to prescribe IR opioids instead of ER/LA opioids and to reserve ER/LA opioids only for severe, continuous pain, avoiding intermittent or as-needed (PRN) use. As noted by the CDC, these recommendations do not preclude the use of ER/LA opioids as an effective treatment in appropriate patient groups. In addition, the updated 2022 guidelines state that: *"The recommendations related to opioid dosages are not intended to be used as an inflexible, rigid standard of care; rather, they are intended to be guideposts to help inform clinician-patient decision-making" and instead states"…before increasing total opioid dosage to ≥50 MME/day, clinicians should pause and carefully reassess evidence of individual benefits and risks."*

One of the primary reasons for release of the 2016 CDC guidelines and changes in state and payer policies was the increasing rates of opioid overdoses, including opioid overdose-related mortality, as well as HCP's concerns regarding misuse and addiction in their patients. The opioid epidemic has been described to occur in 3 waves. The first wave involved prescription opioids,

the second wave involved heroin, and the third, current wave, involves synthetic opioids, primary illicitly synthesized fentanyl and its analogs. The first wave began in the 1990s with a tripling of opioid prescriptions (Kolodny et al., 2015) and subsequent misuse/abuse of prescription opioids and opioid overdoses (Ciccarone, 2017; Ciccarone, 2019; Ciccarone, 2021; Volkow & Blanco, 2021). The second wave corresponded to the period following peak supply of prescription opioids (approximately 2010). Subsequent to a decrease in availability of prescription opioids, overdoses due to heroin began to accelerate in 2011 (Cicero et al., 2012). Whereas opioid overdose deaths from 2000 – 2010 and from 2010 – 2015 were due primarily to prescription opioids and heroin, respectively, the more recent increase in opioid-related mortality has been due primarily to illicitly manufactured fentanyl and its analogs (CDC, 2022). Among the 78,828 opioid-related overdose deaths documented in the 12 months ending in March 2022, 89% were linked to synthetic opioids, most commonly, fentanyl and fentanyl analogs (Ahmad et al., 2023). However, CDC recently announced that for the first time since 2018, there was a decrease in opioid-related overdose deaths from 2022 to 2023, including synthetic opioids (primarily fentanyl; from 76,226 to 74,702) and natural/semi-synthetic opioids (from 12,135 to 10,171) (https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2024/20240515.htm).

Overall, many of the changes in both the prescribing practices for opioid analgesic products, including ER/LA opioids, as well as changing patterns of illicit opioid abuse and overdose occurred prior to or during the primary data collection periods of observational studies 3033-1 and 3033-2, as illustrated in Figure 24. The data sources did, however, predate the release of the updated 2022 CDC guidelines (Dowell et al., 2022). These changes in medical practice and in illicit markets are relevant considerations for interpretation of the data collected in these studies.

Figure 24: Chronology of Studies' 3033-1 and 3033-2 Data Collection in the Context of Changes in Opioid Prescribing and Abuse/Mortality



CDC = Center for Disease Control and Prevention; ER = extended-release; IR = immediate-release; VA = Veterans Affairs
* Data collection period for Study 3033-1: Prospective, Aug 2017 – Oct 2021; Cross-sectional, Sep 2017 – Feb 2019
** Data from Oct 2006 – Dec 2017 used in Study 3033-2.
Note: Drug overdose deaths were identified using ICD-10 codes. Deaths involving more than one opioid category were counted in both categories. Natural/semisynthetic opioids include drugs such as morphine, oxycodone, and hydrocodone; and synthetic opioids other than methadone include drugs such as fentanyl, fentanyl analogs, and tramadol. Deaths may involve more than one drug.
Source: Prescription opioid data: IQVIA®; Opioid-involved mortality: NATIONAL CENTER FOR HEALTH STATISTICS, Data Brief 491. Drug Overdose Deaths in the United States, 2002–2022.

7. CONCLUSIONS

Conclusions that can be drawn from Study 3033-1 include:

- Prescription opioid misuse (intentional use for therapeutic purposes outside label directions or other than prescribed or directed by prescriber), was common among patients with long-term use of opioid analgesics for the treatment of chronic pain.
- The rate of new onset moderate-to-severe OUD among patients with chronic pain prescribed opioids long-term was estimated to be ~ 2% when using the pain-adjusted

measure employing DSM-5 criteria that was developed for this study (may be referred to elsewhere as “PRISM-5-OP OUD”).

- Study 3033-1 (cross-sectional sub-study) found a past-year prevalence of moderate-to-severe OUD of 2.7% using the pain-adjusted measure.
- The factors associated with the strongest and most consistent increases in risk for prescription opioid misuse or abuse, or OUD were pre-existing SUDs or other pre-existing problematic opioid use behaviors.

Conclusions that can be drawn from Study 3033-2 include:

- Initiation of long-term opioid use marked the onset of a multi-year period of continued use of opioids (approx. 80% of the cohort) and other medications usually considered to put patients at risk for complications of opioid therapy.
- There was a continued occurrence of OOD for at least 5 years after opioid initiation (0.5% per year in the 4 study sites).
- Higher baseline dose of opioids was strongly associated with higher subsequent risk of OOD.
- Prior diagnoses of mental health disorders, particularly SUDs, and medications used to treat these disorders, were associated with elevated risk of OOD.
- Use of ER/LA opioids was strongly associated with high-dose opioid regimens, posing a challenge to efforts to disentangle the effects of formulation and dose.

The observational studies were suited to the purpose of the PMRs and the studies addressed evidence gaps related to long-term opioid analgesic use. Validated research measures for misuse, abuse, and addiction were developed and the validity of an existing database algorithm for OOD was confirmed. The incidence of the 5 outcomes related to long-term opioid use in patients with chronic pain was quantified and many prespecified demographics/characteristics were evaluated and the strongest potential risk factors for the outcomes were identified. The risks and risk factors identified in Studies 3033-1 and 3033-2 were broadly consistent with those previously reported in the scientific literature. The studies added a coordinated, validated, large-scale set of findings.

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9. APPENDICES

9.1. Supplemental Data for Study 3033-1

9.1.1. Supplemental Data for the 3033-1 Prospective Study

9.1.1.1. POMAQ Scoring Algorithm

Summaries of POMAQ items that led to positive assessments of either misuse or abuse in Study 3033-1 are provided in Figure 25 and Figure 26, respectively. Note that selection of one of the below criteria led to a positive assessment of misuse or abuse in the study, contributing to the incidence and prevalence estimates. A copy of the final POMAQ survey instrument, including the clinical scoring algorithm can be found at https://www.tandfonline.com/doi/suppl/10.1080/03007995.2022.2065139?scroll=top.

Figure 25: Summary of POMAQ Items Leading to Misuse Designation

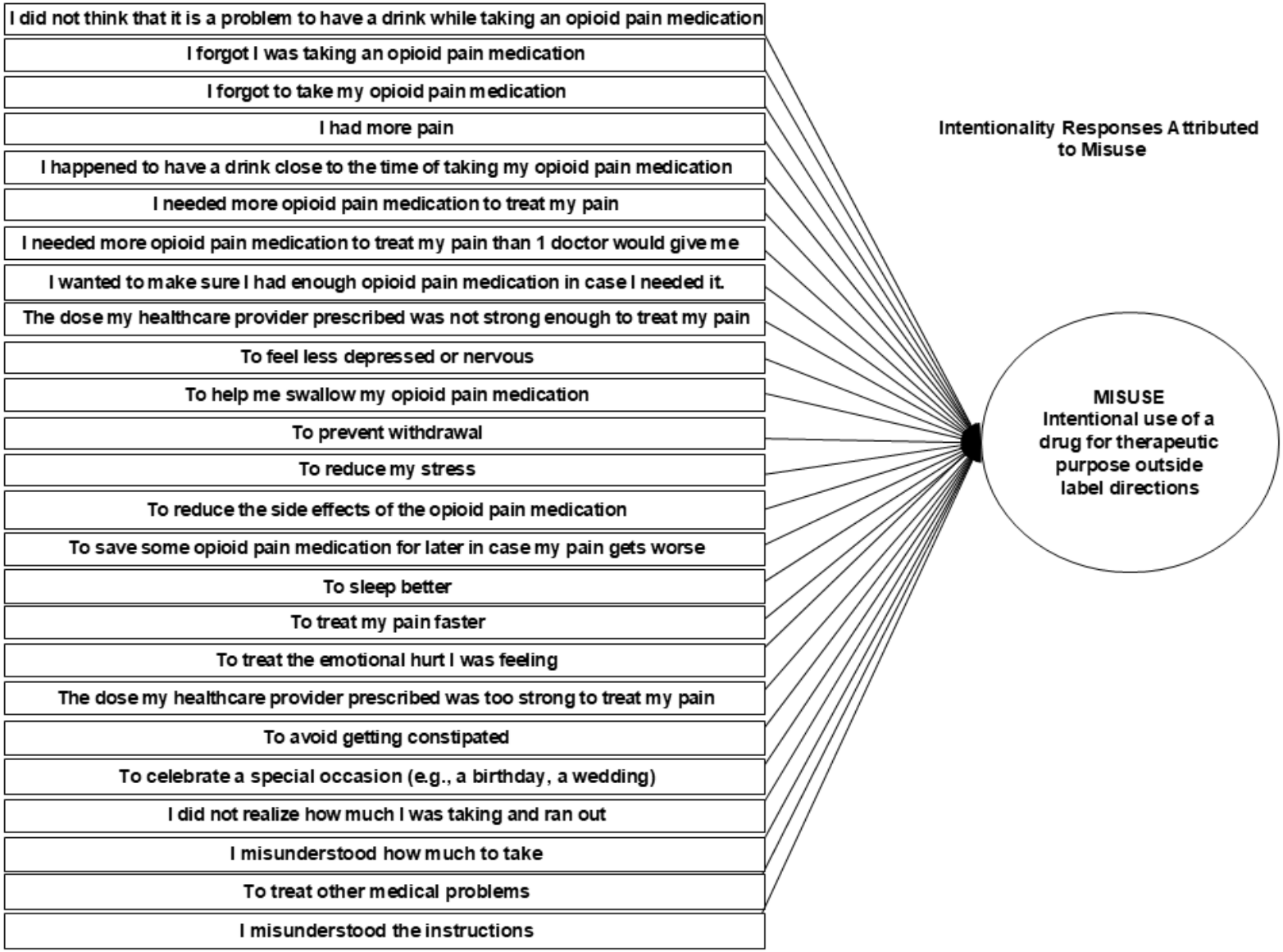
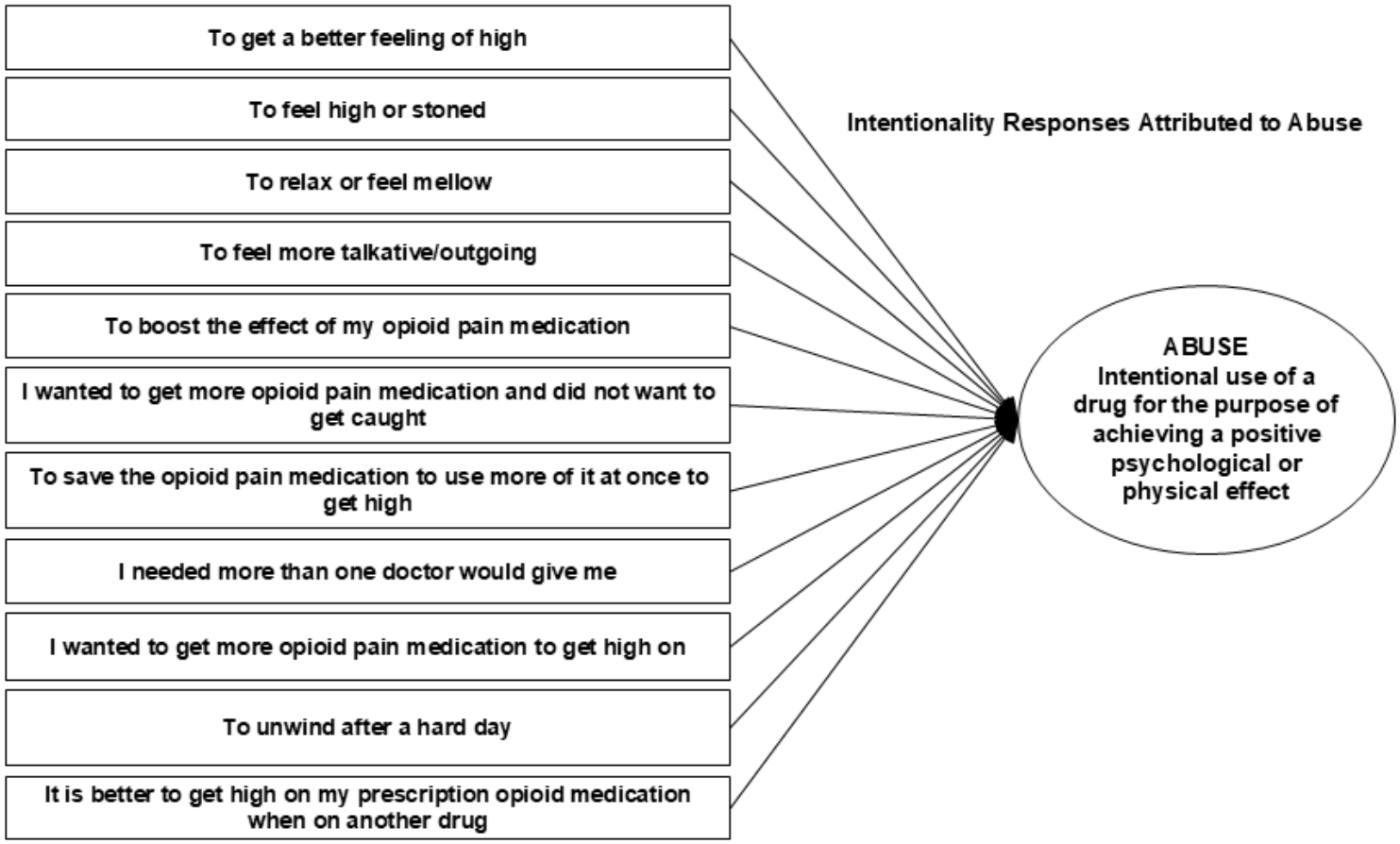


Figure 26: Summary of POMAQ Items Leading to Abuse Designation



9.1.1.2. 3033-1 Prospective Study - Multiple Imputation (MI) Sample

ER/LA Initiators:

Compared to the fully-adjusted prescription opioid misuse model in the complete case analysis sample, the following results were no longer significant in the MI sample: ED visits and past-year non-opioid and non-nicotine SUDs. Variables that were not significant in the complete case sample but associated with increased odds of misuse in the MI sample included: being ≥60 years old, having a baseline MME of 90 – 119 per day, using antipsychotics, having any college education, and having prior-to-past-year non-opioid and non-nicotine SUDs.

Compared to the fully-adjusted prescription opioid abuse model in the complete case analysis sample, the following additional significant variables were associated with increased odds of abuse in the MI sample: being overweight, being obese, and having any college education. Being of Hispanic ethnicity and using stimulants were associated with decreased odds of abuse in the MI sample.

All factors that were significant in the complete case analysis remained significantly associated with OUD in the MI sample, with the exception of having an Elixhauser score of ≥ 2 and PTSD.

LtOT Initiators:

Compared to the fully-adjusted prescription opioid misuse model in the complete case analysis sample, the fully-adjusted MI sample showed several factors that were not previously associated with increased odds of misuse, including antidepressants use, sedative hypnotics use, having less than a high school degree, having PTSD, and a 1-unit increase indicating a change for the worse in pain severity. In addition, the following factors were associated with reduced odds of misuse in the MI sample: having 1 inpatient stay and having an income between $75,001 and $100,000.

Compared to the fully-adjusted prescription opioid abuse model, the MI sample revealed that some factors previously associated with abuse in the complete case analysis sample were no longer significant, including having a dose of 90 – 119 MMEs, being obese, and having parental history of substance use. Being overweight was associated with increased odds of abuse in the MI sample, while receiving care only in an integrated health system was associated with reduced odds of abuse.

Compared to the fully-adjusted OUD model, the fully-adjusted OUD model in the MI sample showed that antidepressants use and being Black were no longer associated with increased odds of OUD, while being Hispanic and having pain interference were associated with increased odds of OUD in the MI sample. Having any college education was associated with reduced odds of OUD in the MI sample.

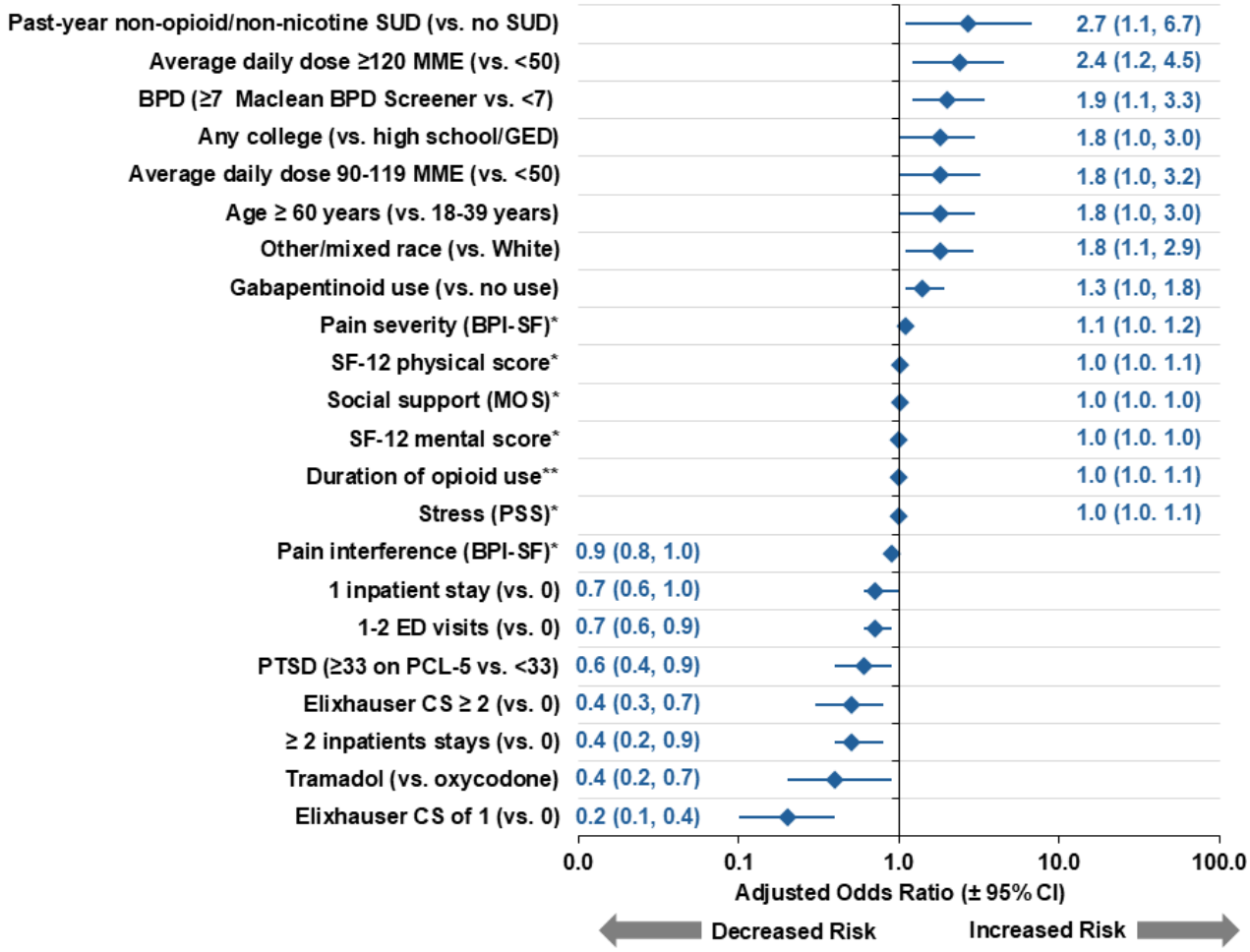
9.1.1.3. 3033-1 Prospective Study –Potential Risk Factors that were Statistically Significant in the Fully-Adjusted Models

9.1.1.3.1. Primary Outcomes (Misuse, Abuse, and Opioid Use Disorder)

Forest plots for statistically significant ($p < 0.05$) risk factors for the primary outcomes in the fully-adjusted models are provided for ER/LA Initiators in Figure 27 (prescription opioid

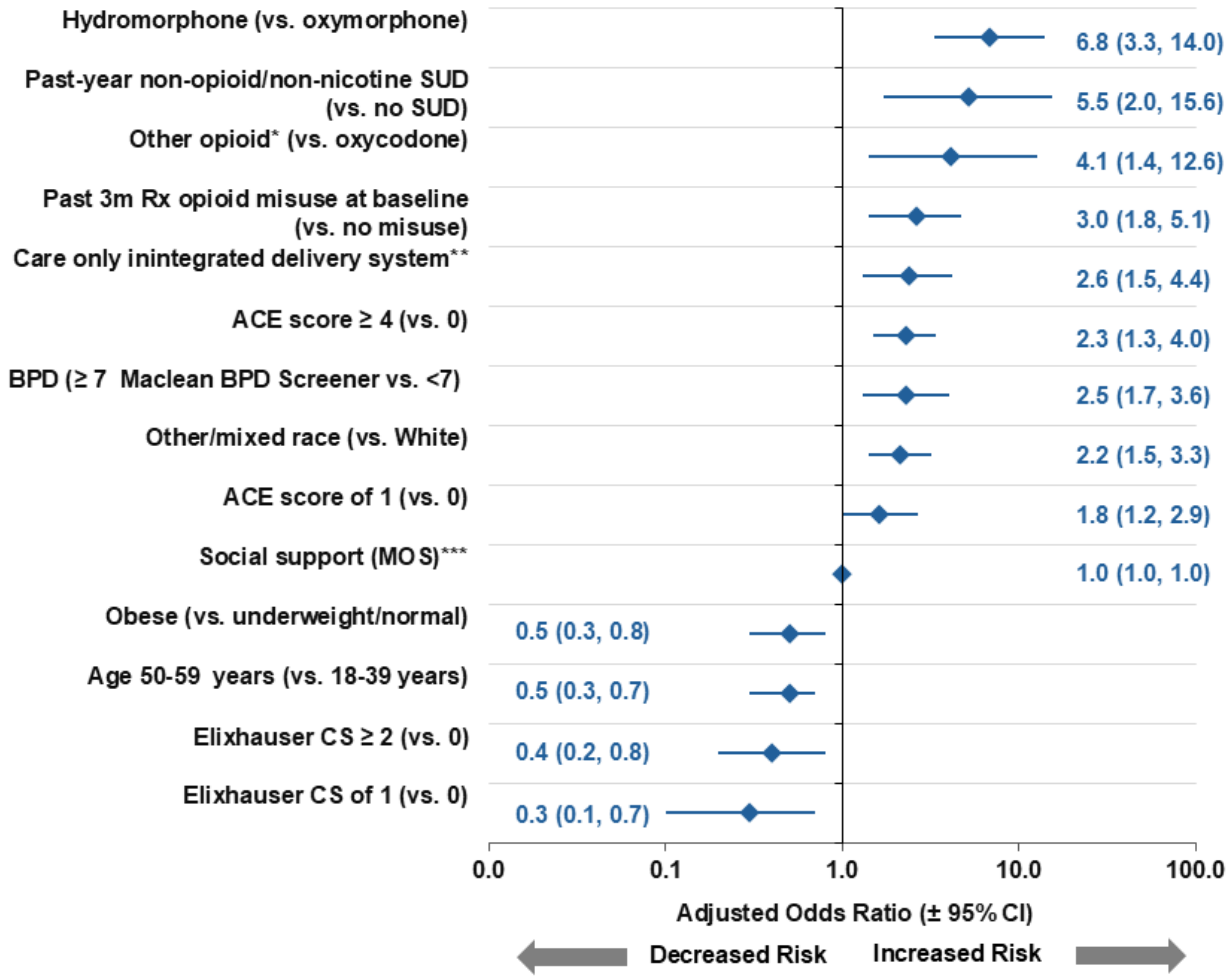
misuse), Figure 28 (prescription opioid abuse), and Figure 29 (OUD), and for LtOT Initiators in Figure 30 (prescription opioid misuse), Figure 31 (prescription opioid abuse), and Figure 32 (OUD).

Figure 27: Statistically Significant (p < 0.05) Potential Risk Factors for Prescription Opioid Misuse – ER/LA Initiators in Study 3033-1 – Prospective Study



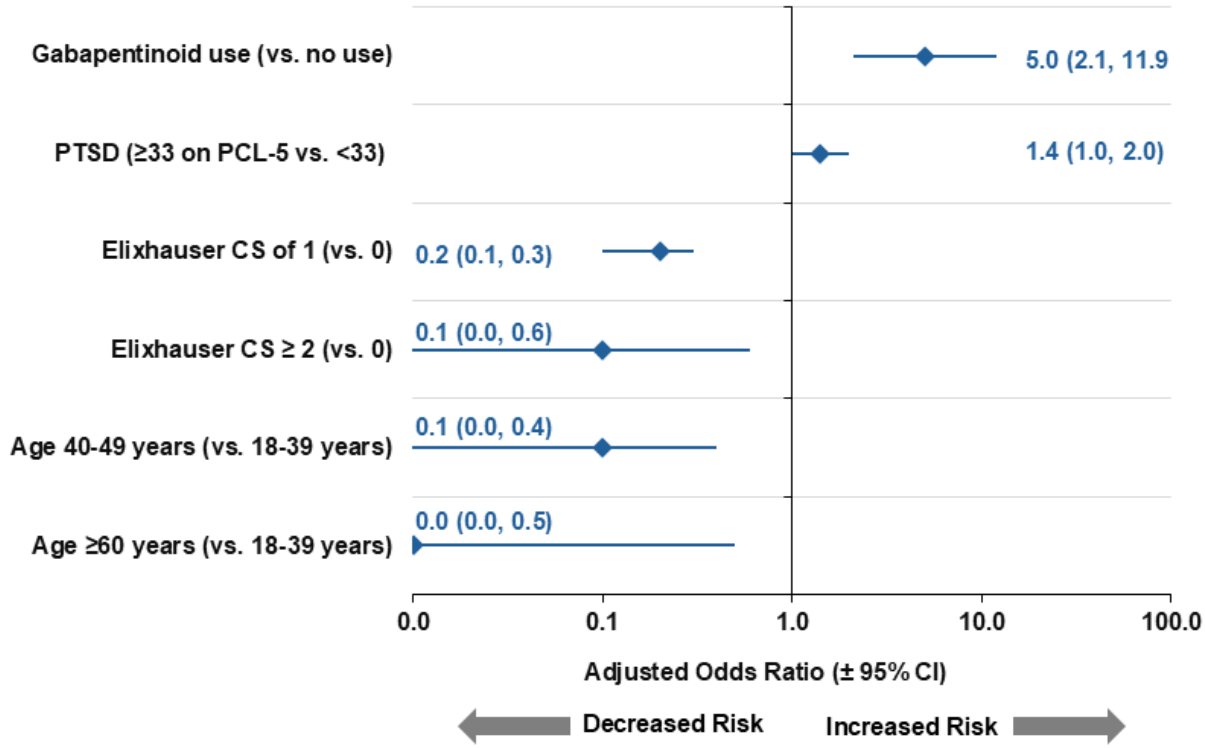
BPD = borderline personality disorder; BPI-SF = Brief Pain Inventory – Short Form; CI = confidence interval; CS = comorbidity score; ED = emergency department; ER/LA = extended-release/long-acting; MME = morphine milligram equivalents; MOS = Medical Outcome Survey; PCL-5 = Post-Traumatic Stress Disorder Checklist for DSM-5; PSS = Perceived Stress Scale; PTSD = post-traumatic stress disorder; SF-12 = 12-item Short Form Health Survey; SUD = substance use disorder.
* Per 1 unit change for the worse.
** Per 7-day increase in duration of opioid use.

Figure 28: Statistically Significant (p < 0.05) Potential Risk Factors for Prescription Opioid Abuse – ER/LA Initiators in Study 3033-1 – Prospective Study



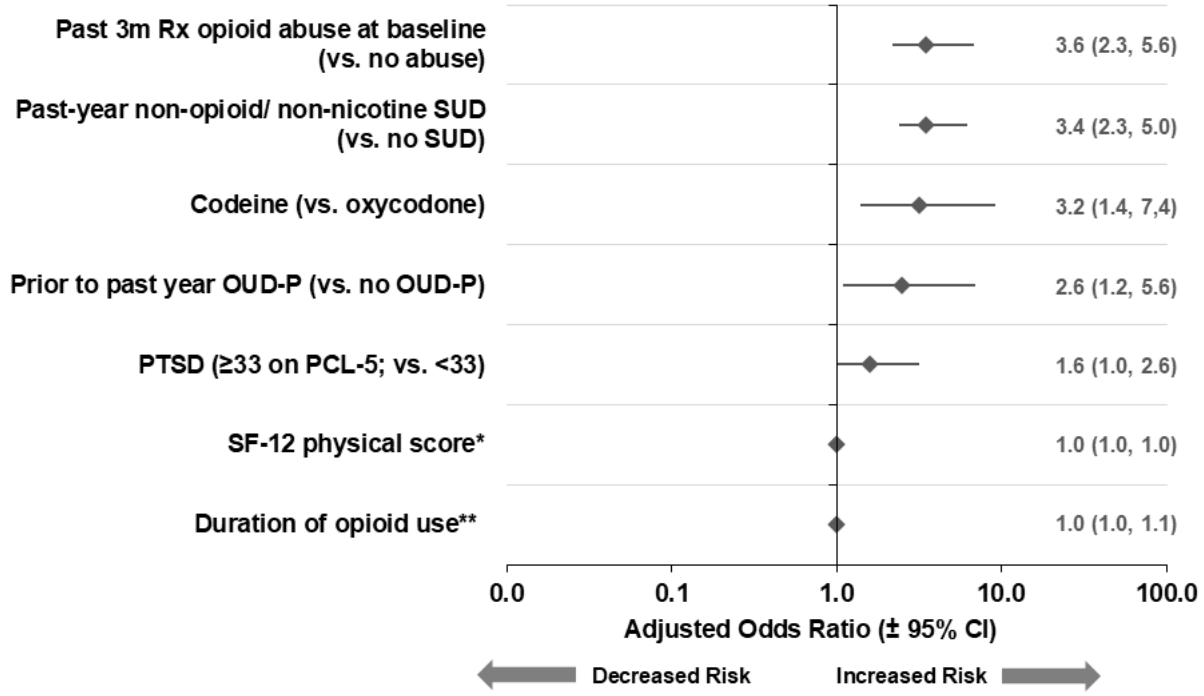
ACE = Adverse Childhood Experiences; BPD = borderline personality disorder; CI = confidence interval; CS = comorbidity score; ER/LA = extended-release/long-acting; m = months; MOS = Medical Outcomes Survey; SUD = substance use disorder.
* When an opioid moiety contained 2 or fewer events for the given outcome, it was collapsed into the "Other" category for the respective outcome.
** vs. care and insurance in an integrated delivery system.
*** Per 1 unit change for the worse.

Figure 29: Statistically Significant (p < 0.05) Potential Risk Factors for Opioid Use Disorder – ER/LA Initiators in Study 3033-1 – Prospective Study



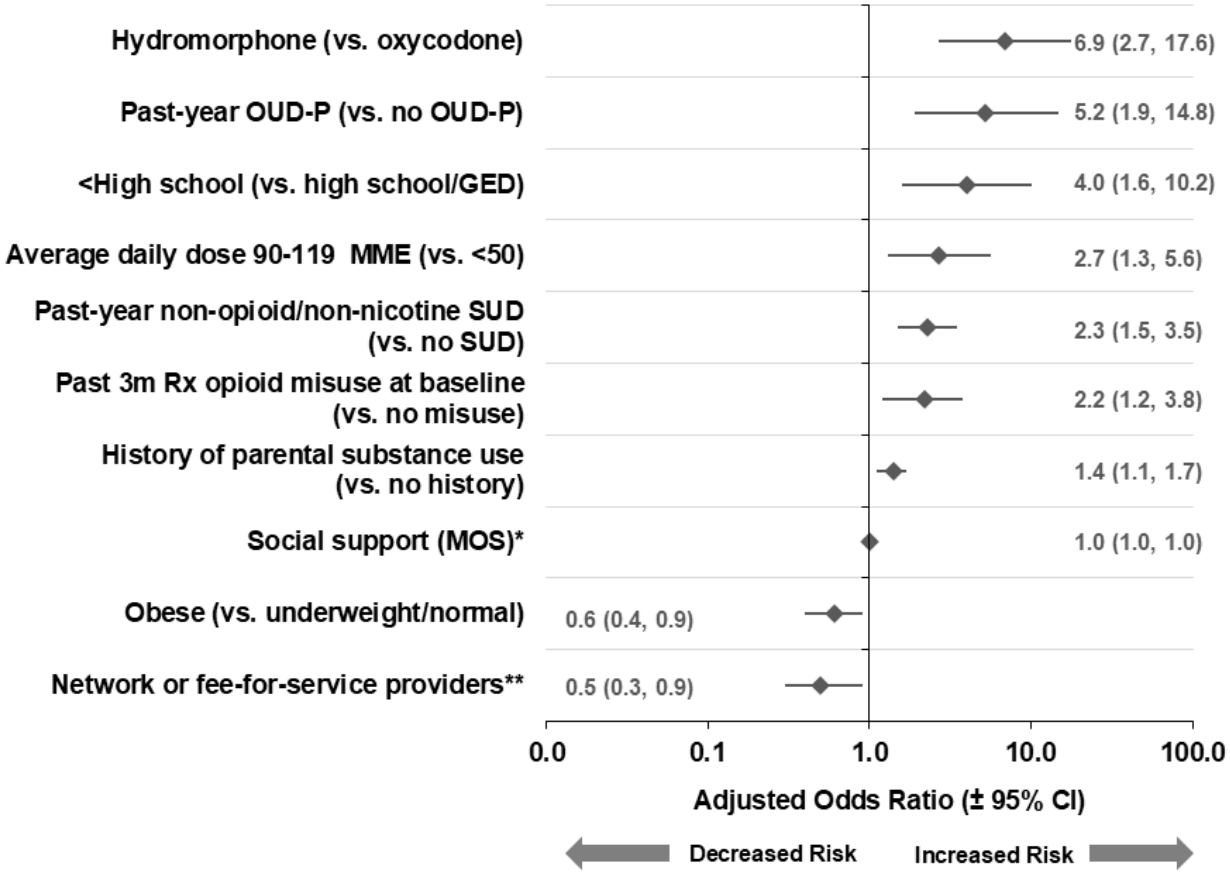
CI = confidence interval; CS = comorbidity score; ER/LA = extended-release/long-acting; PCL-5 = Post-Traumatic Stress Disorder Checklist for DSM-5; PTSD = post-traumatic stress disorder.

Figure 30: Statistically Significant (p < 0.05) Potential Risk Factors for Prescription Opioid Misuse – LtOT Initiators in Study 3033-1 – Prospective Study



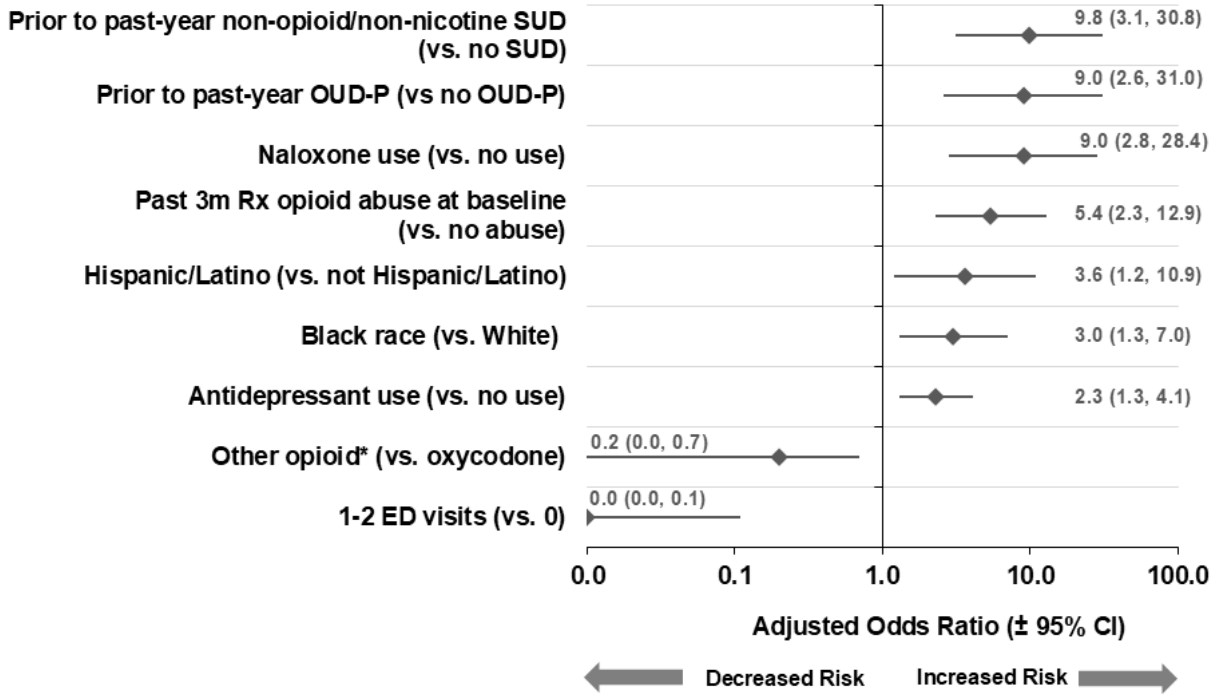
CI = confidence interval; LtOT = long-term opioid analgesic therapy; m = month; OUD-P = opioid use disorder involving prescription opioids; PTSD = post-traumatic stress disorder; SF-12 = Short Form Health Survey; SUD = substance use disorder.
* Per 1 unit change for the worse.
** Per 7-day increase in duration of opioid use.

Figure 31: Statistically Significant (p < 0.05) Potential Risk Factors for Prescription Opioid Abuse – LtOT Initiators in Study 3033-1 – Prospective Study



CI = confidence interval; GED = general equivalency degree; LtOT = long-term opioid analgesic therapy; m = month; MME = morphine milligram equivalents; MOS = Medical Outcome Survey; OUD-P = opioid use disorder involving prescription opioids; SUD = substance use disorder.
* Per 1 unit change for the worse.
** vs. care and insurance in an integrated delivery system.

Figure 32: Statistically Significant (p < 0.05) Potential Risk Factors for Opioid Use Disorder – LtOT Initiators in Study 3033-1 – Prospective Study



CI = confidence interval; ED = emergency department; LtOT = long-term opioid analgesic therapy; m = month; OUD = opioid use disorder; SUD = substance use disorder.
* Per 1 unit change for the worse.

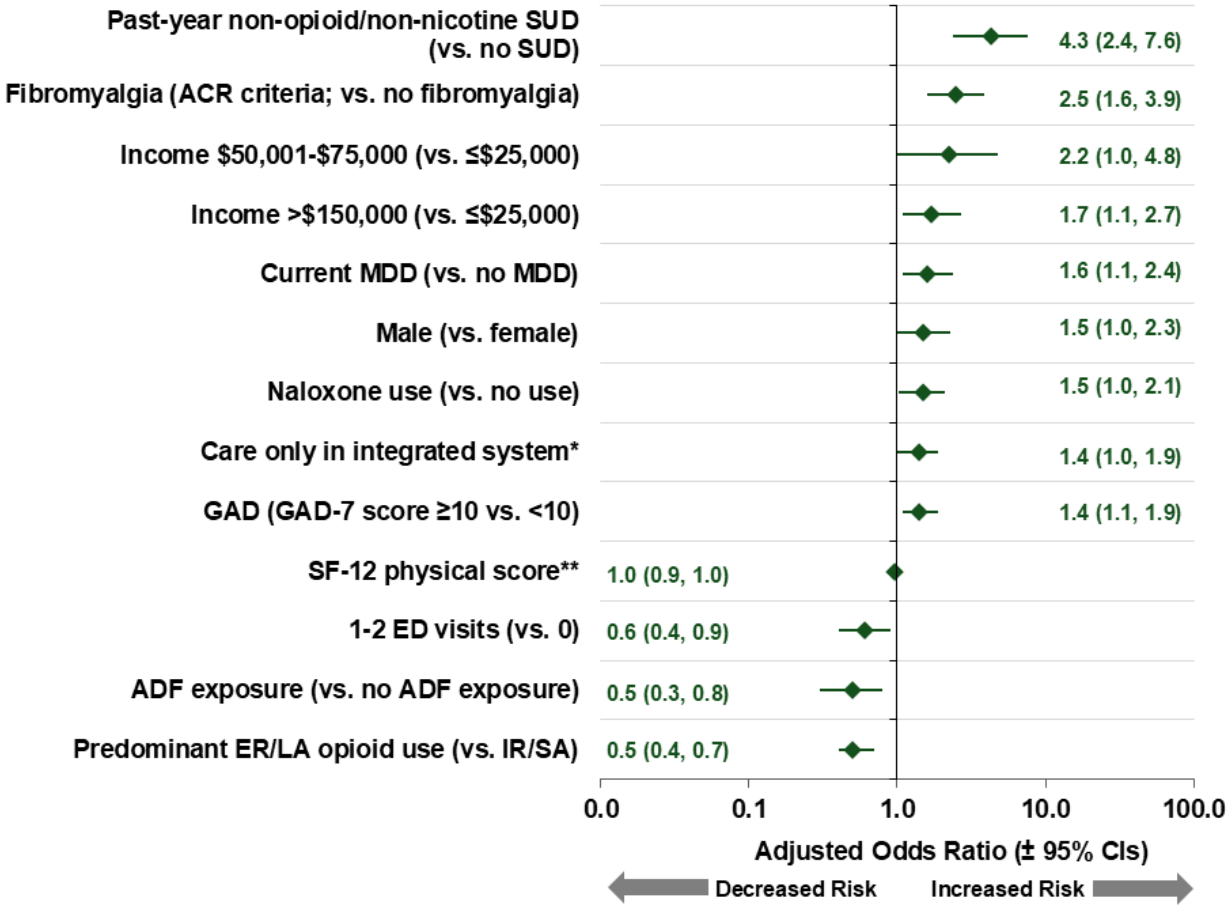
9.1.2. Supplemental Data for the 3033-1 Cross-Sectional Study

9.1.2.1. 3033-1 Cross-Sectional Study – Potential Risk Factors that were Statistically Significant in the Fully-Adjusted Models

9.1.2.1.1. Primary Outcomes (Misuse, Abuse, and OUD)

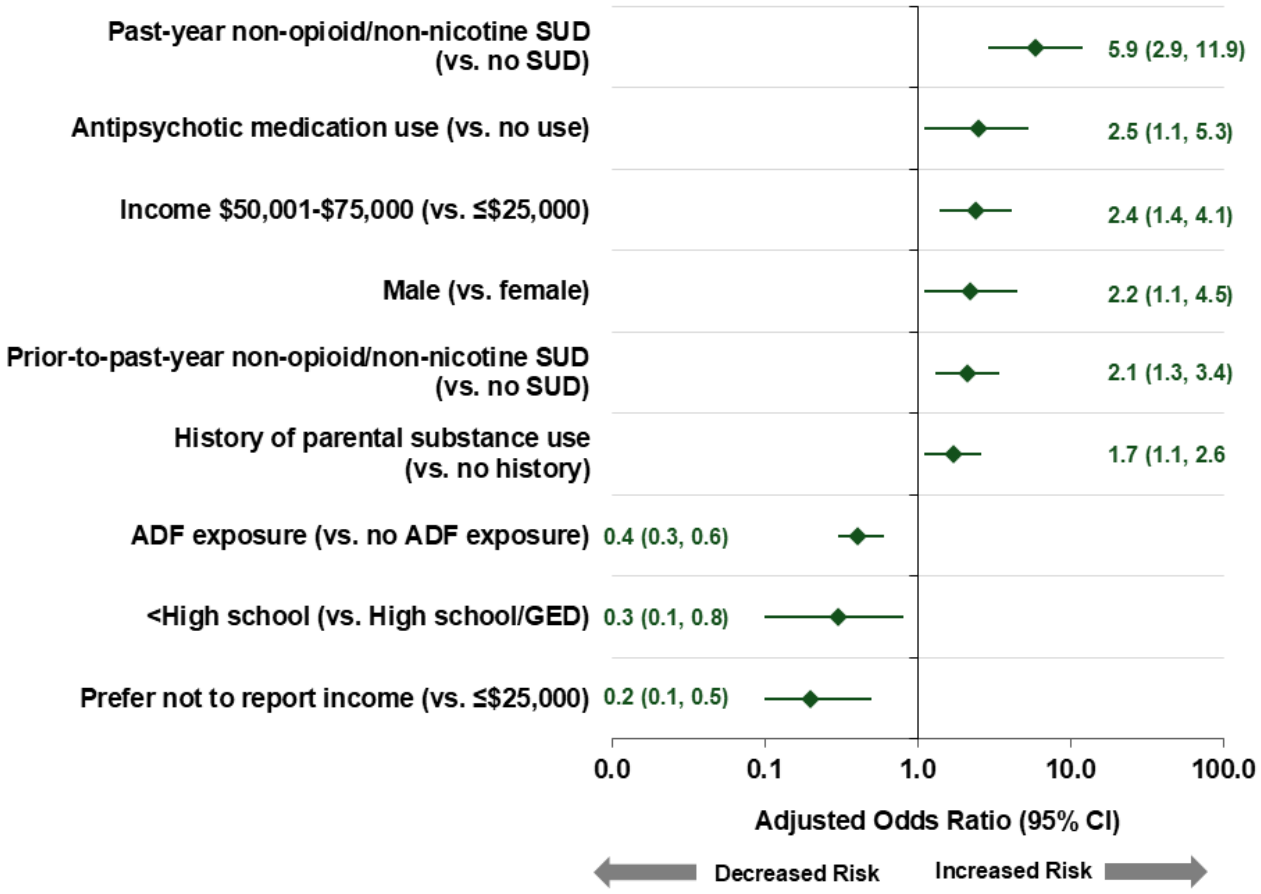
Forest plots for statistically significant (p < 0.05) potential risk factors for the primary outcomes in the fully-adjusted models are provided in Figure 33 (prescription opioid misuse), Figure 34 (prescription opioid abuse), and Figure 35 (OUD).

Figure 33: Statistically Significant (p < 0.05) Potential Risk Factors for Past-3-Month Prescription Opioid Misuse in Study 3033-1 – Cross-Sectional Study



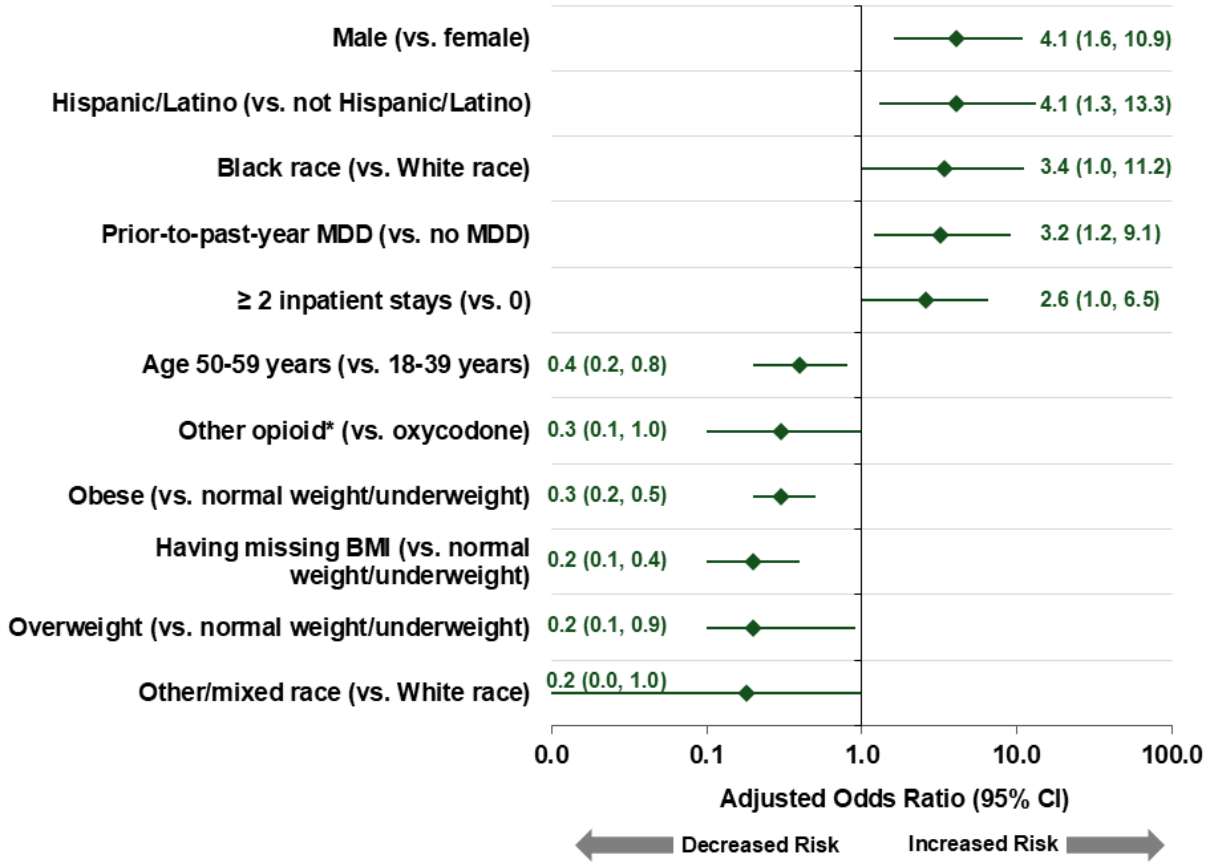
ACR = American College of Rheumatology; ADF = abuse-deterrent formulation; CI = confidence interval; ED = emergency department; ER/LA = extended-release/long-acting; GAD = generalized anxiety disorder; IR/SA = immediate-release/short-acting; SF-12 = Short-Form Health Survey; SUD = substance use disorder.
* vs. insurance and care in an integrated delivery system.
** per 1 unit change for the worse in score.

Figure 34: Statistically Significant (p<0.05) Potential Risk Factors for Past-3-Month Prescription Opioid Abuse in Study 3033-1 – Cross-Sectional Study



ADF = abuse-deterrent formulation; CI = confidence interval; GED = general equivalency degree; SUD = substance use disorder.

Figure 35: Statistically Significant (p<0.05) Potential Risk Factors for Past-Year Opioid Use Disorder in Study 3033-1 – Cross-Sectional Study



ADHD = attention deficit hyperactivity disorder; BMI = body mass index; CI = confidence interval; MDD = major depressive disorder.

9.1.2.2. 3033-1 Cross-Sectional Study – MI Sample

Compared to the fully-adjusted misuse model in the complete case analysis sample, the fully-adjusted prescription opioid misuse model in the MI sample showed that the following potential risk factors were no longer significantly associated with misuse: having had 1 – 2 ED visits; current depression; and naloxone use. Use of muscle relaxers; receiving care only (but not insurance) in an integrated delivery system; and a history of parental substance use were associated with prescription opioid misuse in the MI sample but not in the complete case analysis sample.

Compared to the fully-adjusted prescription opioid abuse model in the complete case analysis sample, the fully-adjusted prescription opioid abuse model in the MI sample included all the same potential risk factors. The following potential risk factors were associated with prescription opioid abuse in the MI sample but not in the complete case analysis sample: having GAD; any college education; and pain interference.

Compared to the fully-adjusted OUD model in the complete case analysis sample, the fully-adjusted OUD model in the MI sample showed that the following risk factors were no longer significantly associated with OUD: being 50 – 59 years of age; being of "other/mixed" race; being overweight; having prior-to-past-year depression; and having ADHD. Further, having had one inpatient stay compared to not having had any was associated with OUD in the MI sample but not in the complete case analysis sample.

9.2. Supplemental Data for Study 3033-2

9.2.1. Study 3033-2 – Supplemental Potential Risk Factor Data for Opioid-Involved Overdose and Opioid Overdose-Related Death (OOD)

Meta-analytic summary HRs for OOD (adjusted for age, sex, calendar era, and Census Region) by principal molecule, diagnosis, and non-opioid medication are provided in Table 11, Table 12, and Table 13, respectively. Meta-analytic summary HRs for OOD from the fully-adjusted model, including Qualification Period MMEs are provided in Table 14.

Table 11: Meta-Analytic Summary Hazard Ratios for Opioid-Involved Overdose and Opioid Overdose-Related Death (OOD) by Principal Molecule (Adjusted for Age, Sex, Calendar Era, and Census Region)

Term	% of Cohort	HR	95% CI		p-value (2-sided)	I^2	Number of Sites
			LB	UB			
Principal Molecule							
Hydrocodone (reference)	58.9%	1.00	-	-	-	-	4
Benzhydrocodone	0.0%	-	-	-	-	-	0
Codeine	0.1%	2.42	0.78	7.54	0.127	0.00	3
Dihydrocodeine	0.0%	-	-	-	-	-	0
Fentanyl	5.1%	1.78	1.21	2.62	0.004	0.53	4
Hydromorphone	1.1%	1.68	0.67	4.21	0.273	0.64	4
Levorphanol	0.0%	-	-	-	-	-	0
Meperidine	0.1%	1.42	0.46	4.42	0.540	0.00	2
Methadone	1.4%	3.14	2.31	4.26	<0.001	0.36	4
Morphine	5.1%	2.20	1.53	3.15	<0.001	0.75	4
Opium	0.0%	-	-	-	-	-	0
Oxycodone	26.4%	1.63	1.37	1.95	<0.001	0.80	4
Oxymorphone	0.8%	2.25	1.46	3.45	<0.001	0.28	4
Tapentadol	0.6%	1.14	0.63	2.08	0.662	0.00	3
Multiple	0.3%	1.75	1.07	2.87	0.027	0.00	2
Principal Molecule Form							
IR/SA (reference)	83.9%	1.00	-	-	-	-	4
ER/LA	15.9%	2.12	1.84	2.45	<0.001	0.42	4
Multiple	0.2%	1.52	0.82	2.83	0.187	-	1
Schedule III History							
Any dispensing of Schedule III opioids from 2006 to cohort entry	14.6%	1.24	1.04	1.47	0.019	0.66	4

CI = confidence interval; ER/LA = extended-release/long-acting; HR = hazard ratio; I^2 = Higgins and Thompson heterogeneity index; IR/SA = immediate-release/short-acting; LB = lower 95% confidence bound; OOD = opioid-involved overdose or opioid overdose-related death; UB = upper 95% confidence bound.
" - " – Indicates that value was not obtained because there was no corresponding exposure at the study site, or because value was not calculated for the reference level. When an exposure was not present for a site, that site did not contribute to the count of sites.
The principal molecule was the Schedule II opioid chemical entity that contributed the most MMEs to the course of therapy that qualified a person for entry into the cohort. The chemical entity and the form of the principal molecule were tabulated separately.

Table 12: Meta-Analytic Summary Hazard Ratios for Opioid-Involved Overdose and Opioid Overdose-Related Death (OOD) by Diagnosis (Adjusted for Age, Sex, Calendar Era, and Census Region)

Term	% of Cohort	HR	95% CI		p-value (2-sided)	I^2	Number of Sites
			LB	UB			
Pain Diagnoses							
Back	56.9%	1.36	1.07	1.74	0.012	0.88	4
Neck	22.1%	1.47	1.36	1.59	<0.001	0.00	4
Limb, extremity, joint	57.3%	1.19	1.10	1.28	<0.001	0.08	4
Fibromyalgia	9.4%	1.70	1.53	1.89	<0.001	0.00	4
Headache	15.9%	1.49	1.30	1.71	<0.001	0.38	4
Orofacial, ear, TMJ	1.5%	1.36	1.07	1.72	0.012	0.00	4
Abdominal bowel	27.2%	1.56	1.44	1.68	<0.001	0.00	4
Urogenital, pelvic, menstrual	6.6%	1.22	0.85	1.76	0.275	0.70	4
Musculoskeletal chest	21.0%	1.54	1.17	2.03	0.002	0.67	4
Neuropathy	9.8%	1.64	1.48	1.83	<0.001	0.00	4
Systemic disorders	5.1%	1.41	1.23	1.63	<0.001	0.00	4
Other	20.8%	2.25	1.96	2.59	<0.001	0.60	4
Fractures, contusions, sprains, strains	26.1%	1.34	1.13	1.58	0.001	0.77	4
SUD Diagnoses							
Alcohol Use Disorder	5.0%	3.11	2.38	4.07	<0.001	0.76	4
OUD	3.6%	4.23	3.82	4.69	<0.001	0.00	4
Other SUD	6.0%	4.02	3.44	4.70	<0.001	0.58	4
Psychiatric Diagnoses							
Psychosis	8.1%	3.28	2.30	4.69	<0.001	0.93	4
Depression	26.5%	2.34	2.06	2.66	<0.001	0.63	4
Anxiety	25.4%	2.30	2.14	2.48	<0.001	0.00	4
Other mental health	2.4%	1.83	1.53	2.20	<0.001	0.00	4

CI = confidence interval; HR = hazard ratio; I^2 = Higgins and Thompson heterogeneity index; LB = lower 95% confidence bound; OOD = opioid-involved overdose or opioid overdose-related death; OUD = opioid use disorder; SUD = substance use disorder; TMJ = temporomandibular joint; UB = upper 95% confidence bound.
Each term has been modeled as present or absent. "Absent" (not shown) is the reference level.
Diagnoses from the diagnostic groups of pain, substance use disorder, and psychiatric disorders between 2006 and Cohort Start Date.

Table 13: Meta-Analytic Summary Hazard Ratios for Opioid-Involved Overdose and Opioid Overdose-Related Death (OOD) by Non-Opioid Medication (Adjusted for Age, Sex, Calendar Era, and Census Region)

Term	% of Cohort	HR	95% CI		p-value (2-sided)	I^2	Number of Sites
			LB	UB			
Antipsychotics	5.9%	2.82	1.97	4.05	< 0.001	0.90	4
Antidepressants	34.1%	2.07	1.65	2.59	< 0.001	0.86	4
Benzodiazepines	31.5%	2.10	1.63	2.69	< 0.001	0.90	4
Hypnotics/sedatives	13.7%	1.76	1.43	2.18	< 0.001	0.81	4
Muscle relaxants	31.7%	1.30	1.21	1.40	< 0.001	0.00	4
Gabapentinoids	20.6%	1.57	1.34	1.83	< 0.001	0.52	4
OUD medications	0.6%	2.95	2.19	3.98	< 0.001	0.00	3
ADHD medications	4.9%	1.90	1.44	2.49	< 0.001	0.74	4

ADHD = attention-deficit/hyperactivity disorder; HR = hazard ratio; I^2 = Higgins and Thompson heterogeneity index; LB = lower 95% confidence bound; OOD = opioid-involved overdose or opioid overdose-related death; OUD = opioid use disorder; UB = upper 95% confidence bound.
Medications dispensed in the 90-day Qualification Period. When an exposure was not present for a site, that site did not contribute to the count of the sites.

Table 14: Meta-Analytic Summary Hazard Ratios for Opioid-Involved Overdose and Opioid Overdose-Related Death (OOD) in the Fully-Adjusted Model (Including Adjustment for Qualification Period MME) from Study 3033-2

Term	HR	95% CI	p-value (2-sided)	I^2	Number of Sites
Age					
18 – 24 years	1.92	(1.07, 3.44)	0.029	0.93	4
25 – 34 years	1.30	(0.95, 1.78)	0.107	0.86	4
35 – 44 years	1.09	(0.90, 1.32)	0.382	0.68	4
45 – 54 years (reference)	1.00	-	-	-	-
55 – 64 years	0.92	(0.83, 1.02)	0.128	0.00	4
65 – 79 years	0.87	(0.71, 1.07)	0.192	0.45	4
Sex					
Female	1.00	-	-	-	-
Male	1.03	(0.95, 1.12)	0.447	0.00	4
Baseline Opioid Dose (Total Qualification Period MMEs)					
< 1,500 MMEs (reference)	1.00	-	-	-	-
1,500 to < 2,500 MMEs	1.59	(1.21, 2.09)	0.001	0.60	4
2,500 to < 3,500 MMEs	1.60	(1.39, 1.84)	< 0.001	0.00	4
3,500 to < 6,000 MMEs	1.84	(1.49, 2.27)	< 0.001	0.22	4
≥ 6,000 MMEs	2.69	(2.31, 3.13)	< 0.001	0.00	4
Principal Molecule					
Hydrocodone (reference)	1.00	-	-	-	-
Methadone	1.65	(1.00, 2.74)	0.051	0.69	3
Morphine	1.46	(1.11, 1.91)	0.007	0.33	2
Principal Molecule Form					
IR/SA (reference)	1.00	-	-	-	-
ER/LA	1.00	(0.87, 1.16)	0.953	0.00	4
Baseline Medications (Dispensed During the Qualification Period)					
Antipsychotics	1.43	(1.18, 1.73)	< 0.001	0.40	3
Benzodiazepines	1.57	(1.34, 1.84)	< 0.001	0.66	3
Antidepressants	1.36	(1.18, 1.57)	< 0.001	0.52	4

Term	HR	95% CI	p-value (2-sided)	I^2	Number of Sites
SUD Diagnosis					
OUD	1.58	(1.40, 1.79)	< 0.001	0.00	3
Other SUD	1.77	(1.58, 1.98)	< 0.001	0.00	3
Alcohol use disorder	1.66	(1.23, 2.23)	0.001	0.70	4
Other Diagnoses					
Psychosis	1.48	(1.13, 1.93)	0.004	0.81	4
Depression	1.25	(1.13, 1.39)	< 0.001	0.23	4

CI = confidence interval; ER/LA = extended-release/long-acting; HR = hazard ratio; I^2 = Higgins and Thompson heterogeneity index; IR/SA = immediate-release/short-acting; OOD = opioid-involved overdose and opioid-overdose-related death; OUD = opioid use disorder; MMEs = morphine milligram equivalents; SUD = substance use disorder.
The reference category for the principal molecule variables in the meta-analysis was hydrocodone plus, in each site, the molecules that were not statistically distinguishable from hydrocodone at $p < 0.10$ in stepwise regression.

9.3. Validation Studies

9.3.1. Instrument Validation Studies for PMR 3033-1: PMR 3033-3, PMR 3033-4, and PMR 3033-5

9.3.1.1. PMR 3033-3: A Qualitative Study to Assess the Content Validity of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ): Qualitative Report of Cognitive Interviews

Study 3033-3 was a qualitative, cognitive interview study to ensure that the content and questions of the draft POMAQ were understandable to patients and relevant to their experiences. Study 3033-4 was a cross-sectional validation study for the POMAQ, and Study 3033-5 was a validation study for the PRISM-5-OP diagnostic interview for OUD.

Prior to launching the qualitative study, OPC's Observational Studies Workgroup (OSW) and FDA-invited experts reviewed an existing instrument, the SR-MAD, to revise the measure to include additional questions regarding misuse and abuse behaviors, and to meet the objective of the PMR for Study 3033-1. Given these modifications, the questionnaire's name was changed to the POMAQ. A copy of the final POMAQ survey instrument can be found at https://www.tandfonline.com/doi/suppl/10.1080/03007995.2022.2065139?scroll=top. PMR

3033-3: A Qualitative Study to Assess the Content Validity of the POMAQ: Qualitative Report of Cognitive Interviews

PMR 3033-3 is described as follows:

> *A prospective observational study designed to assess the content validity and patient interpretation of the POMAQ. Patient understanding of the concepts of misuse and abuse will also be obtained.*

Methods and results of Study 3033-3 are described in more detail in Coyne et al., 2021a and Coyne et al., 2023.

The *FDA Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009) emphasizes the importance of conducting qualitative research throughout the process of instrument development to ensure that the content of the measure is consistent with patients' experiences and to ensure that the questions are interpreted as intended and asked in a manner understood by patients. Therefore, the purpose of Study 3033-3 was to evaluate patient understanding of the POMAQ using cognitive interviewing techniques among adults with chronic moderate-to-severe pain.

Study 3033-3 was a cross-sectional, qualitative study involving a one-time in-clinic visit for participants. Participants were recruited from clinical centers using each clinic's patient database or medical records to review the inclusion/exclusion criteria and ensure that potential participants met the criteria and were classified in the appropriate group. Clinical site coordinators either called or approached eligible patients to introduce the study over the phone or in-person using an introductory script. One-on-one cognitive interviews were conducted by trained and experienced staff members of the Contract Research Organization (Evidera).

Recruitment for participants in the qualitative study targeted equal numbers of participants with chronic, moderate-to-severe pain in the following four groups:

- ***Group 1 – Known Opioid Abusers:*** Participants who were currently taking opioids and had a past history of and/or current diagnosis of opioid abuse or SUD.
- ***Group 2 – Known Abusers of Other Substances***: Participants who were currently taking opioids and had a past history of and/or current diagnosis of non-opioid SUD (e.g., alcohol, benzodiazepines).
- ***Group 3 – Non-opioid Abusers:*** Participants who were currently taking opioids and did not have a history of opioid abuse or SUD.
- ***Group 4 – Non-opioid Users:*** Participants who had no knowledge of prior and/or current chronic opioid use and who had no history of opioid abuse or SUD.

Standard guidelines for qualitative research on establishing and reporting content validity of patient-reported outcomes (Patrick et al., 2011a; Patrick et al., 2011b) were used to achieve the objectives. More specifically, participants were asked how they interpreted individual items, ease of completion, the comprehensiveness of the instrument, and the appropriateness of the format, response scales, and recall period. All interviews were conducted in English.

Fifty-six participants with chronic pain were recruited from 6 clinical centers in the US. All participants completed the POMAQ survey on an iPad during their study visit; however, only 54 participants completed the qualitative interviews beyond the introductory questions. Key findings are as follows:

- The qualitative interviews were lengthy as each POMAQ question and response option were cognitively interviewed. Given the length of the interview and this population of patients with chronic pain on prescription opioids, only 21% (n = 12) of all participants completed the full qualitative interview. The interview guide was randomly alternated to start at the end of the POMAQ and go backwards or to start at the beginning and go forwards to ensure at least 7 patients per patient group were interviewed on each question.
- The mean age of participants was 48.7 (2.3) years, and they were predominately female (57.1%) and White (78.6%). Almost half (42.9%) reported being on disability and 25.0% reported full-time employment, while 7.1% reported part-time employment. Level of education varied, with most participants having either some college (46.4%), secondary/high school (23.2%), or a college degree (21.4%) as their highest level of education. No participant had a post-graduate degree.
- Overall, the POMAQ was well-understood and received positive feedback. All but one participant stated they were comfortable completing the POMAQ and none stated concerns about answering the questions honestly. A few participants (11%) did express concerns about completing the POMAQ using a secure internet site as they either were not computer savvy (5.4%) or were concerned about internet security (5.4%).
- While all participants stated they were honest when completing the POMAQ, 51% did not think others would be honest when completing the POMAQ.

Minor wording modifications were made to the POMAQ questions to address concerns or issues noted by the participants and to enhance clarity and understanding of the POMAQ. Overall, participants understood the intention of the questions.

Overall, the POMAQ demonstrated content validity among patients with moderate-to-severe chronic pain who were taking prescription opioids. Thus, the POMAQ was considered ready for quantitative validation among a larger cohort of patients with chronic pain.

9.3.1.2. PMR 3033-4: POMAQ Validation

PMR 3033-4 is described as follows:

> *An observational study to evaluate the validity and reproducibility of the POMAQ, which will be used to identify opioid abuse and misuse behaviors among participants who have chronic pain which requires long-term opioid analgesic use.*

More details regarding the methods and results of Study 3033-4 can be found in Coyne et al., 2021b; Coyne et al., 2021c, and Coyne et al., 2022.

9.3.1.2.1. Objectives and Methodology

Study 3033-4 was a cross-sectional validation study that assessed the validity and reproducibility of the POMAQ to identify opioid abuse and misuse behaviors among participants with chronic pain that requires long-term opioid use, and to identify patterns of behaviors that commonly co-occur within individuals.

Patients seen at various clinics within 5 DoD/TriCare clinics located across the US who were identified through claims data as having refilled a prescription opioid within the prior 3 months were recruited to participate in the study. Each patient completed a battery of questionnaires including: the POMAQ, Brief Pain Inventory-Short Form (BPI-SF), Prescription Drug Use Questionnaire – Patient version (PDUQp), Socially Desirable Response Set Five-item Survey (SDRS-5), Medical Outcomes Study: 36-item Short Form Health Survey Instrument (MOS SF-36), and sociodemographic questions. Patients were also asked to provide a urine and hair (optional) sample during the study visit.

Participants (≥ 18 years) had been diagnosed with a chronic pain condition (≥ 3 months), which required long-term treatment with opioids, and were willing and able to provide informed consent, and complete assessments, including the urine sample. Participants were excluded if they had cognitive or other impairment, a terminal illness (life expectancy < 6 months), or were active-duty service members of the military.

After completing the POMAQ survey, participants were asked to take part in a telephone interview with a mental health expert to ascertain abuse, dependence, or addiction using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) Substance Use Disorders Module.

A total of 3,263 potential participants were screened, of whom 938 (28.7%) were eligible, consented, and enrolled; 1,588 (48.7%) declined, 604 (18.5%) were ineligible, and 133 (4.1%) were eligible but not enrolled (due to site oversight and lost to follow-up). The POMAQ survey was completed by 809 (86.2%) enrollees; 51.1% (n = 479) consented to provide hair; however, only 90.4% of hair consent providers had enough hair to provide a hair sample.

9.3.1.2.2. Summary of Findings

Mean (SD) age of the sample who completed the POMAQ was 55.4 (12.7) years; with slightly more than half being female (55.5%), and the majority being non-Hispanic/Latino (90.6%), and White/Caucasian (74.8%). Most participants had long-term chronic pain, with a mean (SD) duration of 14.7 (10.5) years and had been treated for pain by a physician for 11.7 (9.4) years. The most common pain conditions (not mutually exclusive) were lower back pain (76.6%), neck or shoulder pain (60.3%), and osteoarthritis (38.7%). The most frequently prescribed current opioid pain medications were oxycodone (35.7%), tramadol (34.5%), and hydrocodone (26.9%). More than half (54.8%) of participants were currently taking one opioid and 45% were taking ≥ 2 opioids. Health status was assessed using the MOS SF-36 and BPI-SF. Participants' health status was relatively poor as assessed by the MOS SF-36, particularly in the "role physical" domain. Participants' pain severity and pain interference status were moderate as assessed by the BPI-SF.

Key findings for POMAQ behaviors reported in the PAST YEAR (from date of POMAQ completion) yielded a range of prevalence from 0% (purchasing or stealing a prescription pad) to 45.7% (took less or were unsure they took less than their prescribed opioids), with many behaviors falling in the 2 to 20% range.

EHR data supported patient responses from the POMAQ. There was high resource utilization among this chronic pain patient population; almost all participants (95.8%) visited at least one

outpatient facility in the year prior to study participation (mean [SD] of 33.4 [29.3] visits), and ER visits were reported by 40.8% of participants. The mean (SD) number of opioid-prescriptions filled per person over the past year was 15.4 (8.2).

Construct validity of the POMAQ responses were supported by corroborating responses on the PDUQp and POTQ V2. Similar strong evidence was found among the SCID-I interviews with the majority of patients with current substance use abuse or dependence also reporting the use of the substance on the POMAQ.

The POMAQ had excellent test-retest reliability between the first and second administration in a randomized subgroup of patients, with percent agreement in item responses ranging from 87.8% to 100%.

The clinical scoring algorithm for the POMAQ was developed and validated in a cohort of 60 patients using EHR records, and further refined to reflect clinically relevant patient behaviors identified by expert review (Coyne et al., 2022). The POMAQ clinical algorithm classified participants as having misuse (n = 96), abuse (n = 81), no misuse/abuse (n = 627) behaviors, diversion only (n = 5), or diversion and aberrant signal only (n = 1). Compared to the other groups, the “abuse” group was generally younger, had a greater proportion of participants with kidney problems, had a longer mean duration of being treated for their pain, and had a greater proportion of smokers. The misuse group had a greater proportion of participants with a postgraduate degree and a higher mean duration of time at their clinical practice.

Construct validity of the POMAQ clinical scoring algorithm was supported by MOS SF36 and SDRS-5 scores. Participants classified as having behaviors of misuse and abuse generally had lower MOS SF-36 (poorer health-related quality of life) and SDRS-5 (less socially desirable responses) scores. Pain scores and impact on the BPI-SF were similar across behavior groups.

Overall, Study 3033-4 demonstrated that the POMAQ is a valid, reproducible tool to assess the presence of prescription opioid misuse and abuse behaviors among chronic pain patients currently on prescription opioids. Further evaluation needs to be conducted to assess the longitudinal usefulness of the POMAQ in detecting change in behaviors.

9.3.1.3. PMR 3033-5: Validation of PRISM-5-OP Measure of Addiction to Prescription Opioid Medication

PMR 3033-5 is described as follows:

> *An observational study to validate measures of prescription opioid Substance Use Disorder and addiction in patients who have received or are receiving opioid analgesics for chronic pain.*

More details regarding the methods and results of Study 3033-5 can be found in Hasin et al., 2022.

9.3.1.3.1. Objectives and Methodology

In 2013, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) SUD diagnosis was reformulated into 11 criteria across alcohol and other substances, a change

supported by extensive evidence. Although the 11 criteria formed a unidimensional continuum, a diagnostic threshold was needed due to the requirements of the field for a binary (yes/no) diagnosis. To avoid a marked perturbation in prevalence rates without justification, the work group set the threshold at 2 or more criteria because this threshold produced the best agreement in prevalences in general population and clinical samples between DSM-5 SUD criteria and DSM-IV substance abuse and dependence disorders combined (Hasin et al., 2013). Additionally, severity levels were defined with 2 – 3 criteria representing mild SUD, 4 – 5 criteria representing moderate SUD, and ≥ 6 criteria representing DSM-5 SUD diagnoses at the severe end, or addiction.

However, little evidence was available on the 11 DSM-5 SUD criteria as applied to OUD/addiction among patients prescribed opioids to treat chronic pain. In such patients, the possibility existed that accurately diagnosing addiction to prescription opioids would require incorporation of additional information from the patients about positively endorsed criteria to adjust the diagnostic algorithms. The PRISM is a diagnostic interview with strong reliability and validity that has been used as a gold standard in other studies. At the time of PMR issuance, the PRISM-5 was the only computer-assisted diagnostic interview that assessed DSM-5 criteria. A specifically tailored version of the PRISM-5, the PRISM5-OP, was created for use in Study 3033-1. The PRISM-5-OP instrument was designed to evaluate DSM-5 SUD/addiction to prescription opioids in patients taking prescription opioids to treat chronic pain and was created by making the following changes to the PRISM interview:

- The prescription opioid module was moved to the beginning.
- Questions were added on participants' history of prescription opioid use.
- Probes and adjustments were added based on therapeutic vs. non-therapeutic intent.

Thus, the primary objective was to validate PRISM-5-OP measures of DSM-5 SUD/addiction to prescription opioids, including the comparative validity of diagnoses and dimensional measures with and without adjustments for patients with chronic pain. Adjustments to the criteria in the PRISM-5-OP incorporated information from participants on their opioid use (i.e., as prescribed vs. more/other than as prescribed) to adjust the physiological criteria, withdrawal and tolerance, and on the intent of their behaviors (therapeutic, i.e., to treat pain vs. non-therapeutic, e.g., to get high; Table 15) for DSM-5 SUD/addiction behavioral criteria.

Table 15: Reasons for DSM-5 SUD Behavioral Criteria

No.	Reasons for DSM-5 Symptom Behaviors	Intent
1	To relieve physical pain	Therapeutic
2	To feel high	Non-therapeutic
3	To feel less depressed, nervous, or angry	Non-therapeutic
4	To help you sleep (other than relieving pain so you could sleep)	Non-therapeutic
5	To prevent or treat withdrawal (feeling sick after the medication wore off)	Non-therapeutic
6	To feel relaxed or mellow	Non-therapeutic
7	Because you saw something that reminded you of the medication	Non-therapeutic

The primary outcomes were the PRISM-5-OP DSM-5 criteria, dimensional measures, and diagnoses of DSM-5 SUD/addiction to prescription opioids. These measures were:

- ***Unadjusted measure***: 11 DSM-5 criteria were rated positive if present, without regard for "use as prescribed" or pain.
- ***DSM-5 measure***: withdrawal and tolerance criteria were not rated positive (i.e., were adjusted) if they occurred among participants who used opioids as prescribed, as defined in DSM-5. The DSM-5 measure may be referred to elsewhere as "DSM-5-OUD definition of OUD".
- ***Pain-adjusted measure***: in addition to the DSM-5 adjustment, DSM-5 behavioral criteria were rated positive only if additional patient information from the PRISM-5-OP instrument indicated that the criteria represented addiction indicators (non-therapeutic intent) rather than treatment of pain (therapeutic intent). The pain-adjusted measure may be referred to elsewhere as "PRISM-5-OP OUD".

The secondary objective was to evaluate the test-retest reliability of the PRISM-5-OP measures. Tertiary objectives were:

- To provide information about interview length, acceptability to participants, and item clarity and frequencies to facilitate adjustment of PRISM-5-OP prior to Study 3033-1; to explore concordance with the POMAQ.
- Explore concordance of reasons for use ascertained in PRISM-5-OP and in self-report.

Two groups of participants were evaluated:

a) ***Pain clinic patients***: those in medical treatment who had a current prescription for opioids to treat chronic pain (recruited from 4 university-affiliated, medically well-managed pain or rehabilitation medicine clinics).

b) ***Substance Treatment Center patients***: those in treatment for addiction who had a prescription for opioids to treat chronic pain (recruited from 2 university-affiliated addiction treatment settings).

Participants (aged ≥ 18 years) were English-speaking and must have had a prescription for opioids to treat chronic pain for ≥ 30 days. Participants were excluded if they had a cognitive impairment, or hearing/vision impairment that precluded completion of the assessments or provision of informed consent.

PRISM-5-OP interviews and self-administered questionnaire (SAQ) data were collected via cross-sectional evaluations of 606 participants (February 2016 to April 2017), with re-test interviews conducted 1 – 14 days later, on a subset of 206 participants. Data were extracted from medical records and Longitudinal Expert All Data (LEAD) clinician reviews were conducted on of a subset of 100 participants.

Validation was done in steps, examining unadjusted and adjusted measures, to determine: (a) test-retest reliability of the 11 individual criteria, and dimensional and dichotomous measures created from the 11 criteria; (b) internal structure of the 11 criteria (internal consistency, factor structure, differential item functioning [DIF]); (c) agreement of PRISM-5-OP measures with ratings made by expert clinicians who had additional information (LEAD procedure); (d) differential distribution of unadjusted and adjusted criteria, dimensional scores and dichotomous diagnostic ratings in high-risk and low-risk patients; (e) MultitraitMultimethod (MTMM) results to validate the unadjusted and adjusted measures and compare their validity (including history of treatment for addiction, tampering with opioid medication, personal history of DSM-5 SUD, family history of drug use disorder, personal history of psychiatric comorbidity, pain level, and legitimate use of prescription opioid medication for pain).

9.3.1.3.2. Summary of Findings

Test-Retest Reliability:

Test-retest reliability was moderate to substantial for all binary unadjusted criteria (κ = 0.43 – 0.63) and adjusted criteria (κ = 0.44 – 0.69) and dichotomized diagnoses (κ = 0.37 – 0.66). Reliability was excellent for the 11 criteria combined into a dimensional measure (ICC = 0.79 – 0.82).

Dimensionality:

The 11 criteria formed a unidimensional factor, with strong factor loadings for all criteria (range, 0.79 – 0.99). Cronbach's alpha was excellent for unadjusted, DSM-5 and pain-adjusted criteria sets (α=0.92 – 0.95). The pain-adjusted criteria set showed greater total test information (67.1) than the unadjusted set (28.5) or the DSM-5 set (39.8).

Expert Clinician Ratings (LEAD Procedure):

When compared to LEAD expert clinician ratings, most PRISM-5-OP binary ratings (unadjusted and adjusted criteria, diagnoses) showed excellent sensitivity (range, 0.73 – 1.00), specificity (range, 0.79 – 1.00), positive predictive value (PPV; range, 0.68 – 1.00), negative predictive

value (NPV; range, 0.85 – 1.00, and agreement (κ = 0.68 – 0.98), and excellent intraclass correlation coefficients (ICC = 0.0.98 – 0.99) for dimensional measures.

Differences Between Patients from Pain Clinics and Substance Treatment Settings:

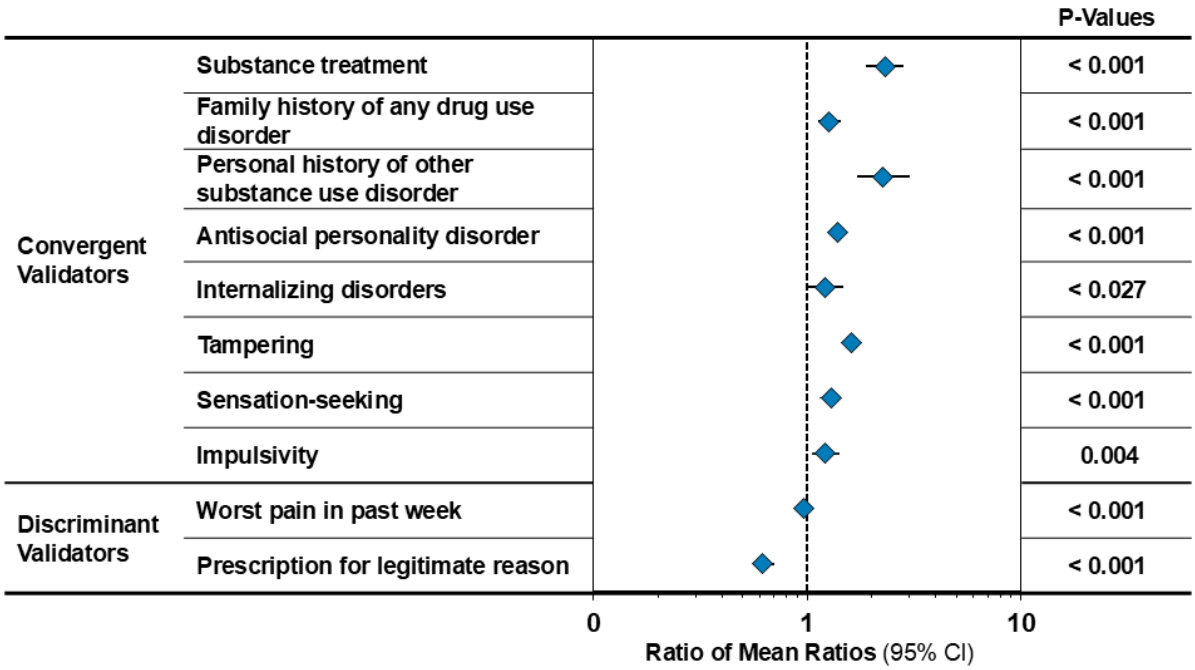
Differences in odds of unadjusted and pain-adjusted criteria and diagnoses were statistically significantly greater in the pain treatment sites than in the addiction treatment sites (p-values = 0.01 to <0.001 for all outcomes except one criterion with p = 0.065), indicating that patients in substance treatment settings often had non-therapeutic reasons (e.g., to get high) for the DSM-5 criteria, which was not often the case for the pain clinic patients.

MTMM Results, Dimensional PRISM-5-OP Measures:

Use of the PRISM-5-OP dimensional measures provided for well-powered analyses. Using the MTMM validators with the PRISM-5-OP dimensional measures as the outcomes showed that the pain-adjusted dimensional measures had statistically significantly stronger associations with all MTMM validators than the unadjusted or DSM dimensional measures in bivariate correlated regression analyses for all validators and in structural equation modeling, for all validators, except personal history of psychiatric comorbidity.

For the convergent validators, associations (represented by mean ratios) were significantly greater with the pain-adjusted measures than with the DSM-5 measures. The mean ratios for the pain-adjusted measures ranged from 1.60 to 5.30, while the mean ratios for the DSM-5 measures ranged from 1.26 to 2.30 (Figure 36). For discriminant validators, the associations for worst pain in the last week were similar using the pain-adjusted and DSM-5 measures, and obtaining the prescription for legitimate reasons was negatively associated with both pain-adjusted and DSM-5 measures. Thus, the strongest findings were from the convergent validators, which all consistently favored the pain-adjusted measures.

Figure 36: Difference in Association of Pain-adjusted and DSM-5 Dimensional Prescription Opioid Use Disorder Diagnostic Measures with Validators in Study 3033-5

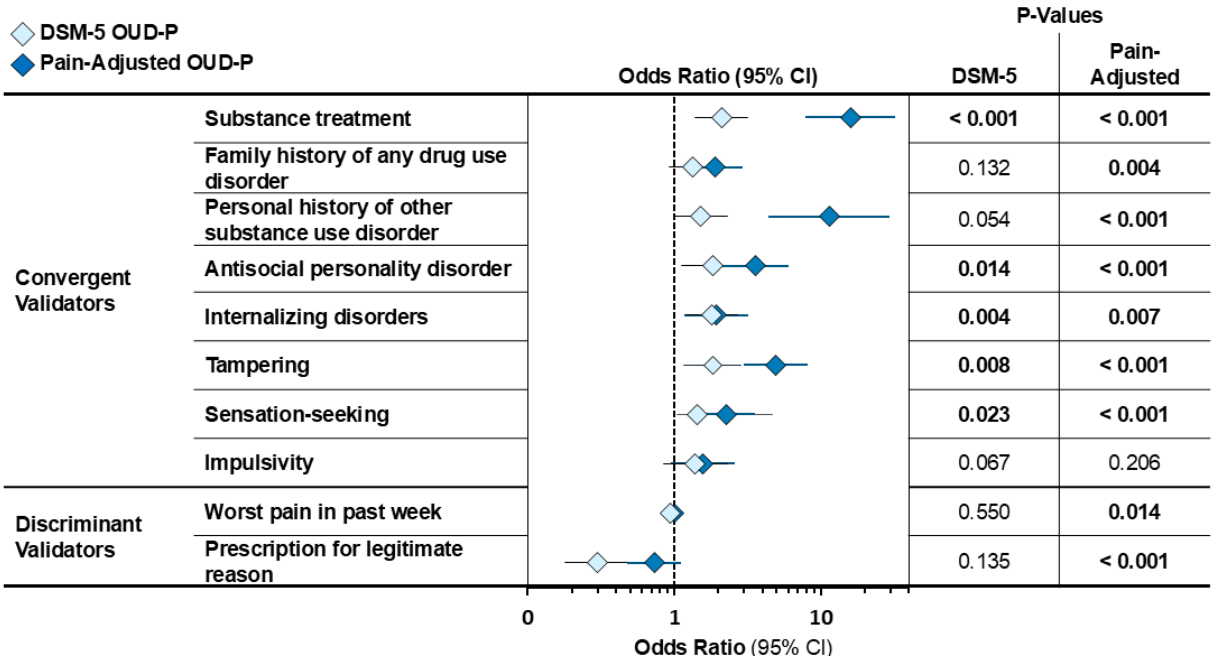


DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; GAD = generalized anxiety disorder; MDD = major depressive disorder; OUD = opioid use disorder; PTSD = post-traumatic stress disorder.
DSM-5: a count of all DSM-5 OUD criteria that occurred, except tolerance and withdrawal, which were counted as positive only among patients using opioids in nonprescribed ways. The DSM-5 measure may be referred to elsewhere as "DSM-5-OUD definition of OUD".
Pain-adjusted: a count of DSM-5 OUD criteria that included the DSM-5 adjustment and, in addition, counted as positive only the criteria that occurred for non-therapeutic reasons (i.e., other than to treat pain, such as to get high).
Notes: Drug use disorder indicates any substance use disorder except alcohol. The pain-adjusted measure may be referred to elsewhere as "PRISM-5-OP OUD".
Internalization disorders include MDD, persistent depression, GAD, and PTSD.
Tampering = Ever tampered with prescribed opioid medication.
The ratio of mean ratios shows the difference in the validator effect for pain-adjusted versus DSM-5 is presented as the ratio of mean ratios. If this term is statistically significantly different from 1, differential effects are present, meaning that one criteria set shows a stronger association than the other.
Source: Hasin et al., 2022.

Diagnostic Threshold:

Selecting an optimal cut-point to dichotomize the dimensional measures proved challenging because the results were very similar across several values of potential diagnostic thresholds. The value of ≥ 4 criteria for the pain-adjusted measure was selected as the diagnostic threshold (0.547 Spearman's correlation for an External Composite Validator vs. ≤ 0.539 for other thresholds; although, there was overlap in the 95% CIs for other thresholds for the pain-adjusted diagnosis). For the convergent validators, associations (represented by ORs) were significantly greater with the pain-adjusted diagnoses than with the DSM-5 diagnoses for 8 of 10 validators (Figure 37).

Figure 37: Associations of Validators with Binary Prescription OUD Diagnoses



CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; GAD = generalized anxiety disorder; MDD = major depressive disorder; OUD = opioid use disorder; PTSD = post-traumatic stress disorder; Rx = prescription; SUD = substance use disorder (other than alcohol).
DSM-5: a count of all DSM-5 OUD criteria that occurred, except tolerance and withdrawal, which were counted as positive only among patients using opioids in nonprescribed ways. The DSM-5 measure may be referred to elsewhere as "DSM-5-OUD definition of OUD".
Pain-adjusted: a count of DSM-5 OUD criteria that included the DSM-5 adjustment and, in addition, counted as positive only the criteria that occurred for non-therapeutic reasons (i.e., other than to treat pain, such as to get high).
Notes: Drug use disorder indicates any substance use disorder except alcohol. The pain-adjusted measure may be referred to elsewhere as "PRISM-5-OP OUD".
Internalization disorders include MDD, persistent depression, GAD, and PTSD.
Tampering = Ever tampered with prescribed opioid medication.
The odds ratio is the exponentiated regression coefficient from the correlated-outcomes logistic regression model, controlling for covariates (age, sex, race, education, marital status, employment, and health insurance).
Note: For continuous measures, the ratio indicates change for a one-unit increase in the scale.
Source: Hasin et al., 2022.

MTMM Results, Dichotomized PRISM-5-OP Measures:

Dichotomized measures reduce power. Fewer results in the MTMM analyses were statistically significant than when using the dimensional PRISM-5-OP measures. However, all results that were statistically significant favored the pain-adjusted measure vs. the unadjusted measure (p-values = 0.034 to < 0.001).

Exploratory/Sensitivity Analyses, Lifetime PRISM-5-OP Measures:

Exploratory/sensitivity analyses using lifetime measures were generally consistent with the results for current measures. In the MTMM analyses of dichotomized lifetime diagnostic

measures, a greater number of significant results favoring the pain-adjusted set were found when current dichotomized measures were analyzed. Lifetime pain-adjusted diagnosis showed statistically significantly greater association with 4 MTMM validators than the DSM-5 diagnosis (p-values = 0.049 – 0.011) and with 5 MTMM validators than the unadjusted diagnosis (p-values = 0.028 – < 0.001). Incorporating whether patients' opioids were ER/LA only or ER/LA plus SA vs. SA only as a control variable did not change results.

Interview Acceptability to Participants:

Despite interview administration time being slightly longer than anticipated, the PRISM-5-OP was very acceptable to participants.

Overall, Study 3033-5 findings indicated that the PRISM-5-OP measures of DSM-5 SUD criteria, dimensional measures, and diagnoses are reliable and valid. After examining differential validity, the strongest empirical support was found for pain-adjusted measures. When administered by appropriately trained and supervised interviewers, the PRISM-5-OP is acceptable to participants, and the data it produces can be used with confidence. Thus, the PRISM-5-OP is a valid measure of DSM-5 SUD/addiction to prescription opioids for use in Study 3033-1.

9.3.2. Algorithm Validation Studies for PMR 3033-02: PMR 3033-6 and 3033-7

9.3.2.1. PMR 3033-6: Study to Validate Coded Medical Terminologies Used to Identify Opioid-Related Overdose in the Post-Marketing Databases to be Employed in PMR Observational Study 3033-2

PMR 3033-6 is described as follows:

> *An observational study to develop and validate an algorithm using coded medical terminologies and other electronic healthcare data to identify opioid-related overdose and death.*

9.3.2.1.1. Objectives and Methodology

Additional information on the methods and results of Study 3033-6 is provided in Green et al., 2019a; Green et al., 2019b, and Hazlehurst et al., 2019.

The purpose of Study 3033-6 was to 1) validate the measurement of OODs and deaths using diagnostic codes alone and diagnostic codes combined with data extracted from clinical text from EHR using NLP, and 2) classify identified OODs and deaths according to whether or not they: were intentional OODs (suicides or attempts); involved heroin; involved substance abuse; involved misuse of prescribed medications; involved provider or patient medication errors; involved anesthesia or inpatient pain management; and/or involved multiple substances. Algorithms that were developed and validated in Study 3033-6 were used in Study 3033-2 among patients prescribed opioid analgesics.

ICD-9 codes for nonfatal diagnoses and ICD-10 codes for fatal events were used in Study 3033-6. In October of 2015, ICD-10 codes replaced ICD-9 codes for nonfatal diagnoses in administrative databases. This study validated existing ICD-9 codes in order to meet the FDA-

required timeline, while ICD-10 diagnostic codes were partially validated as an objective of Study 3033-2.

The primary objectives of Study 3033-6 were:

1. To develop 2 types of algorithms to identify and classify OODs: One type based solely on coded medical terminology to measure OODs (for use in claims-based systems); the other, for use in systems with EHRs, based on coded medical terminology plus medical record text data mined by NLP. The goal was to produce algorithms that are validated for the detection of OOD, differentiation of OOD from opioid-related adverse events, and classification of OODs according to whether or not they involved: substance abuse; patient misuse; inpatient pain management/anesthesia; patient or provider medication-related error; or intentional OODs (suicide/suicide attempts). To achieve these goals, the following were undertaken:
    a. Assessment of the sensitivity, specificity, PPV, and negative predictive value (NPV) of the OOAS code-based algorithm, relative to medical chart audit. This algorithm used medical encounter-based ICD-9 codes to identify OODs and ICD-10 cause-of-death codes to identify opioid-related overdose deaths.
    b. Assessment of the sensitivity, specificity, PPV, and NPV of potential improvements to the OOAS code-based algorithm when additional coded data were added.
    c. Assessment of the sensitivity, specificity, PPV, and NPV of algorithms based on coded data to classify OODs as intentional versus unintentional, and among unintentional OODs, to classify them according to whether or not they were: anesthesia-related/inpatient pain management events; or due to substance abuse, patient misuse of prescribed medications, patient medication error, or provider medication error.
    d. Assessment of the sensitivity, specificity, PPV and NPV of NLP-enhanced algorithms that combined code-based algorithms with NLP-derived determinations based on clinical notes from the EHR, and other non-coded EHR data, to identify and classify OODs.
2. Conduct a portability assessment of the applicability of the OOD and classification algorithms in three healthcare system environments with different healthcare record data.

The secondary objective of the study was to verify the accuracy of ICD-10 opioid-related deaths codes by audit of EHR charts and claims data associated with identified death records.

The OOAS-developed algorithm served as the foundation for this study. A literature review was also conducted to identify new codes or methods that might be used to improve upon the existing algorithm. The initial review found no additional ICD-9 diagnostic or ICD-10 cause-of-death codes not already included in OOAS code-based algorithm. A second review was completed near the end of the study with some additional codes identified and evaluated.

The first algorithms tested used ICD-9 diagnostic and ICD-10 cause-of-death codes alone. Although ICD-10 diagnostic codes did not come into use until after the study period, ICD-10

cause-of-death codes were in use starting in 1999 with continued use throughout the study period. When appropriate, procedure codes, pharmacy records, and other coded data available in claims-based and integrated systems were added and tested. Both of these types of algorithms are referred to as "code-based" algorithms. Natural language processing was used to create NLP-only algorithms as a step toward a third type of algorithm—the "NLP-enhanced" algorithm. The NLP-enhanced algorithms augmented the code-based data with NLP-generated data based on searches of healthcare providers' notes and other clinical text in patients' EHR charts.

The primary study population included all members of KPNW during the period January 1, 2008 through December 31, 2014. From the KPNW population, development and validation samples were created to develop and assess the performance of the algorithms. These samples were comprised of suspected OOD events (i.e., OOD cases identified by the OOD algorithm) and "at-risk" cases (cases with at least 2 diagnoses in the categories of pain, mental health, and substance abuse, each from a different category). The same development and validation samples were used for development and validation of code-based algorithms, NLP-only algorithms, and NLP-enhanced algorithms.

Datasets were created from the development and validation samples for application and assessment of the algorithms. These datasets included coded data, chart audit data, and clinical notes. Events in these datasets represented subsets of each respective sample because adequate data were needed for chart auditors to assess algorithm accuracy and some records did not include adequate data. In addition, machine-readable clinical notes were needed for NLP, thus datasets used for NLP-only algorithm development and validation represented a further subset of those records with adequate chart audit data. Code-based, NLP-only, and NLP-enhanced algorithms were developed using an iterative process. Chart audits assessed accuracy of the algorithm, and auditors gathered additional data from charts which were added to study datasets (e.g., substances involved, intentionality).

To assess the utility of the algorithms in other healthcare systems (portability assessment), 3 healthcare systems were selected: KPW, Optum, and TennCare. This portability assessment covered data over the period January 2008 through December 2014 (December 2013 for TennCare). Portability assessments included application of the NLP-enhanced algorithms in the participating system that had the necessary EHR data and NLP capability (KPW).

As with development and validation work at KPNW, samples for the portability assessment used parallel methods to identify suspected OOD and "at-risk" cases. Samples at portability sites were limited to one event per person to avoid overrepresentation of some individuals in these relatively small samples. Select algorithms were applied to the portability sites based on availability of necessary data.

The primary study population included medical claims at KPNW, medical charts in the EHRs at KPNW, CareEverywhere records for care received outside the KPNW system that were transferred to KPNW member EHRs and reviewed/opened by KPNW members' clinicians (unopened records were not available for review), state death index data for Oregon and Washington, and NDI data. For the secondary portability assessment, data sources included KPW's integrated health system, Tennessee State Medicaid (TennCare) data, and Optum data for insured members with United Health. The primary population of interest was members of the

KPNW integrated healthcare system located in the states of Oregon and southwestern Washington, between 2008 and 2014 (> 475,000 members per year).

A specific focus was on patients prescribed ER/LA opioid analgesics, but all overdose cases in the system were included, then categorized by substances involved, circumstances surrounding, and causes of each overdose. Including all overdose cases allowed us to more accurately specify categorizations made using the algorithms because it increased the sample sizes for development and validation. Had the samples been restricted to those with ER/LA prescriptions, there would not have been an adequate number of overdoses for statistical modeling. Once the algorithms were developed, they were then evaluated among patients prescribed opioids, and sensitivity analyses were used to detect differences in algorithm performance for overdoses among those prescribed ER/LA opioids for 30 days or more and those prescribed ER/LA opioids for less than 30 days.

The primary outcomes were: any OOD, heroin-related overdose events, intentional OODs (suicides and attempted suicides), abuse-related OODs, misuse-related OODs, medication error-related OODs (patient, provider), and opioid-involved polysubstance overdose events

There are no universal standards for algorithm performance based on sensitivity and specificity. Acceptable performance depends on the context and how the algorithms will be used. Sensitivity and specificity were set to 85.0% as acceptable and 90.0% as excellent for the OOD algorithms and the heroin-related overdose classification algorithms, as these were expected to be readily identifiable in medical records. For all other classification algorithms, 75.0% was used for specificity and sensitivity as an acceptable level of performance because it was expected that classification algorithms for abuse, intentionality, misuse, polysubstance involvement, and medication error would be more difficult to develop.

9.3.2.1.2. Summary of Findings

Results showed that the code-based OOD algorithm, originally developed in the OOAS, could not be improved with additional coded data. This algorithm is valid and shows excellent performance in the identification of OOD and opioid-related death across different healthcare environment datasets, including high sensitivity, specificity, PPVs and NPVs, whether it is applied to datasets based on EHRs or those based on insurance claims. Across all sites, sensitivity was greater than 96.0% and specificity was greater than 85.0%. F-scores were greater than 0.92 across all sites, where a score of 1 indicates a model with perfect fit.

Similarly, the code-based algorithm classifying OODs as involving heroin showed excellent performance in the KPNW validation dataset (sensitivity 97.2%, specificity 84.6%) as well as across settings where adequate numbers of heroin-related events were identified to allow analyses.

Identifying intentional OODs (suicides and suicide attempts) was more challenging given the complexity of these events. Nevertheless, the code-based algorithm performed adequately in KPNW in the development dataset and was moved forward to validation. Performance was similar in the validation dataset (sensitivity 70.5%, specificity 90.2%), and the NLP-enhanced algorithm showed statistically significant improvements in performance over the code-based algorithm (sensitivity 78.7%, specificity 91.0%). Statistically, performance of the NLP-enhanced

algorithm was also significantly better in the KPW portability dataset (sensitivity 81.5%, specificity 95.2%) than the code-based algorithm alone (sensitivity 74.1%, specificity 86.7%).

The code-based algorithm developed to detect substance abuse-involved OODs showed moderate performance in the validation dataset at KPNW (sensitivity 75.3%, specificity 79.5%). This was expected given the complexity of identifying substance abuse with codes alone, particularly for stigmatizing disorders such as these. In this context, it was expected that the NLP-enhanced algorithm's performance would improve upon the code-based algorithm, and this was confirmed, with performance significantly better statistically (sensitivity 80.5%, specificity 76.3%) than that of the code-based algorithm. Data were not available to test the NLP-enhanced substance abuse classification algorithm in the other data environments.

In contrast to the successfully developed code-based algorithms, adequate performance was not achieved during development (e.g., sensitivity and specificity were <75%) for algorithms classifying opioids according to involvement of: 1) misuse of prescribed medications, 2) patient errors taking medications, or 3) polysubstance overdose events. NLP-enhanced algorithms were also unsuccessful. In addition, there weren't an adequate number of cases to attempt modeling of clinician prescribing errors. As a result, these classification algorithms were not tested in the validation dataset.

Finally, after identifying few inpatient OODs using the code-based OOD algorithm, the proposed modeling strategy for identifying inpatient pain management/anesthesia-related events was found to be untenable. It was suspected that such events were not being identified by the algorithm, and in response, alternative methods of identifying them were explored. By evaluating hospital medication administration records for anesthesia, narcotic administration, and naloxone administration, a method that performed well for identifying inpatient OOD/oversedation events was developed. Importantly, inpatient events identified showed almost no overlap with those found using the code-based OOD algorithm. This provides preliminary reassurance that these methods detect different, nearly mutually exclusive, types of OOD.

The code-based OOD algorithm showed excellent performance across different systems, indicating that it could be used in Study 3033-2 to accurately identify OODs, as well as more broadly to identify and track OODs and monitor programs designed to curb the opioid crisis. It also accurately classified the subset of OODs involving heroin. Algorithms for classifying intentional and substance abuse-related OODs performed with adequate accuracy for use in some studies, particularly given the complexity of these designations. As such, they should also be considered useful. This is particularly true for the NLP-enhanced algorithms for intentional OODs and abuse-related OODs, which should be applied in settings that have the capacity and data to use NLP.

9.3.2.2. PMR 3033-7: An Observational Study to Develop Computable Algorithms for Identifying Opioid Abuse and Addiction Based on Administrative Claims Data

PMR 3033-7 is described as follows*:*

> *An observational study to develop and validate an algorithm using coded medical terminologies to identify patients experiencing prescription opioid abuse or addiction, among patients receiving an ER/LA opioid analgesic.*

Additional details regarding Study 3033-7 are provided in Carrell et al., 2020.

The primary objectives of the 3033-7 study were to develop and validate a classification model to identify patients experiencing prescription opioid abuse and/or addiction based on medical claims data in patient populations receiving long-term ER/LA opioid therapy, using a high-quality gold standard based on manual chart review to evaluate the model's performance. Secondary objectives of this study were to develop and evaluate a model designed to estimate the onset of prescription opioid abuse/addiction, to develop and evaluate a "best case" model using all available EHR data, to develop and evaluate a simple ICD-9 code-based algorithm, to compare the results of the abuse/addiction algorithm developed as a primary objective to the "best case" and simple ICD-9 models, and to conduct a portability assessment of the classification model developed as a primary study objective.

For purposes of algorithm development, the study population included patients prescribed long-term ER and/or LA opioid analgesics in a healthcare system that had an EHR system that provided ease of access to medical records for chart review. For purposes of assessing the portability of this algorithm to other settings, the study populations included patients meeting the same criteria for receiving long-term ER/LA opioid analgesics and either 1) received care in a healthcare system similar to that used for algorithm development, 2) had medical claims for their care documented in a large medical claims database, or 3) received care through a state Medicaid program in a clinic of a large academic medical center. The study period included all patient data available at study sites between January 1, 2006 and June 30, 2015, inclusive.

A total of 1,126 potential predictors characterizing patient demographics, procedures, diagnoses, timing, dose, and location of medication dispensing were operationalized. The final model incorporating 53 predictors had a sensitivity of 0.582 at PPV of 0.572. ICD-9 codes for opioid abuse, dependence, and poisoning had a sensitivity of 0.390 at PPV of 0.599 in the same cohort.

Despite considerable effort and consideration of a very large number of potential predictors of abuse/addiction, this study did not yield a high-performing automated algorithm for identifying these outcomes based on widely available structured claims data. Nor did the study results yield encouragement that development of such an algorithm is feasible.

9.4. Study-Defined Terms

Note: Description of terms is not intended provide comprehensive definitions for general use, but rather to clarify how terms were used within this document, in reference to the specific PMR 3033 series of observational studies.

Term	Description
Abuse	Defined in Study 3033-1 as the intentional use of a drug for non-therapeutic purposes, repeatedly or sporadically, for the purpose of achieving a positive psychological or physical effect
Addiction	Defined in Study 3033-1 as opioid use disorder, including opioid use disorder involving prescription opioids and/or opioid use disorder involving heroin
Adjusted	Used in reference to adjusted models in the multivariate analysis
Baseline End Date	Defined in Study 3033-2 as the day before the first Schedule II opioid dispensing in the sequence that resulted in ≥ 70 days dispensed in 90 days.
Baseline Period	Defined in Study 3033-2 as the 183-day interval that ended with the Baseline End Date
Cohort End Date	Defined in Study 3033-2 as the earliest of the Administrative End Date (end of site-specific grace period following end of enrollment, or the end of the study period; a non-hospital institutional stay (other than for substance abuse treatment); the day preceding the 80th birthday; death; or opioid-involved overdose or opioid-overdose related death
Cohort Start Date	Defined in Study 3033-2 as the 90th day following the Baseline End Date. This date was also the last day of the Qualification Period.
DSM-5 measure	Used in Study 3033-1 for assessing opioid use disorder, whereby withdrawal and tolerance criteria of the DSM-5 were not rated positive (i.e., were adjusted) if they occurred among participants who used opioids as prescribed, as defined in DSM-5. The DSM-5 measure may be referred to elsewhere as "DSM-5-OUD definition of OUD".
ER/LA Initiator	Cohort of participants in Study 3033-1 with initiation of extend-release/long-acting opioid therapy that included ≥ 28 days' possession of an extended-release/long-acting opioid followed by a subsequent extended-release/long-acting prescription, and no extended-release/long-acting opioid use in the prior 6 months.
LtOT Initiator	Cohort of participants in Study 3033-1 with initiation of long-term opioid analgesic therapy, operationalized as ≥ 70 days of opioid possession over a 90-day window with extended-release/long-acting and/or Schedule II immediate-release/short-acting opioids, and no extended-release/long-acting or Schedule II immediate-release/short-acting opioid use in the prior 6 months.
Misuse	Defined in Study 3033-1 as the intentional use of a drug for therapeutic purpose (to reduce an aversive symptom or state) in a manner that is

Term	Description
	inappropriately outside label directions, or in a manner other than prescribed or directed by an HCP.
OOD	Opioid-involved overdose or opioid overdose-related death – outcome used in Study 3033-2 to assess "overdose", which occurred when either the claims/encounter definition or the National Death Index definition of opioid overdose had been met
OUD classification	≥ 2 criteria – "any OUD" ≥ 4 criteria – "moderate-to-severe OUD" ≥ 6 criteria – "severe OUD"
Pain-adjusted measure	Used in Study 3033-1 to assess opioid use disorder whereby withdrawal and tolerance criteria of the DSM-5 were not rated positive if they occurred among participants who used opioids as prescribed, and the behavioral DSM-5 criteria were rated positive only if patient information from the PRISM-5-OP instrument indicated that the criteria represented addiction indicators (non-therapeutic intent) rather than treatment of pain (therapeutic intent). The pain-adjusted measure may be referred to elsewhere as "PRISM-5-OP OUD".
Principal Molecule	Principal molecule – the Schedule II opioid chemical entity in Study 3033-2 that contributed the most morphine milligram equivalents to the course of therapy that defined the Baseline End Date and Cohort Start Date.
Qualification Period	Period in Study 3033-2 starting from the day after the Baseline End Date through 90 days during which there was a qualifying course of therapy, characterized by at least 70 days dispensed of Schedule II opioids
Secondary	Refers to any analyses that are not primary or exploratory – including pre-specified or post-hoc analyses.
Switch/Add Date	Date of the dispensing in Study 3033-2 that qualified a person for the Switch/Add Cohort
Unweighted/weighted	Used in reference to "crude" (unweighted) and adjusted (weighted) incidence/prevalence