OPTIMIZING THE PUBLIC HEALTH BENEFIT OF A MEDICAID CONTROLLED SUBSTANCE LOCK-IN PROGRAM

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ABSTRACT

Andrew W. Roberts: Optimizing the Public Health Benefit of a Medicaid Controlled Substance Lock-In Program
(Under the direction of Joel F. Farley and Asheley C. Skinner)

Medicaid controlled substance lock-in programs (MLIP) have garnered increased attention for their potential role in combating prescription drug abuse. MLIPs are purported to enhance care coordination for high-risk beneficiaries by restricting access to a single prescriber and pharmacy for controlled substance service coverage. However, the MLIP evidence base is largely non-existent. The purpose of this dissertation was to examine two threats to MLIP effectiveness: lock-in circumvention through out-of-pocket purchases and lack of standardized MLIP eligibility criteria. Our aims were to investigate: 1) the effect of enrollment in the North Carolina (NC) MLIP on controlled substance circumvention behavior, 2) prescription-level characteristics of circumvented opioid analgesics, and 3) optimal claims-based measures of high-risk opioid use for assessing MLIP eligibility.

We used a retrospective cohort of NC MLIP enrollees and linked NC Medicaid claims and Controlled Substances Reporting System data from 10/1/2009-9/30/2012. Generalized estimating equations estimated the effect of MLIP enrollment and covariates on circumvention behavior (Aim 1). Subjects were 3.6 times more likely to obtain a controlled substance prescription through circumvention after MLIP enrollment. Generalized linear models estimated the association of MLIP enrollment with circumvention of opioids with high-risk prescription-level attributes (Aim 2). Mean prescribed daily opioid dose and the likelihood of a circumvented prescription containing a Schedule II opioid product or a long-acting opioid product did not increase after MLIP enrollment.

Medicaid claims data for cross-validation cohorts of opioid users in NC Medicaid were used to test and validate optimal measures of high-risk opioid use (Aim 3). The highest performing dichotomous

predictors of overdose were selected using survival receiver operating characteristic models and bivariate Cox model fit. The best measures were ≥5 opioid claims and ≥12 daily milligram morphine equivalents over 60 days, but these exhibited low sensitivity in capturing subjects with overdose.

MLIP enrollment induced people to circumvent Medicaid to obtain controlled substance prescriptions, negating the underlying purpose of the MLIP intervention. Also, current MLIP eligibility assessment strategies performed poorly in selecting beneficiaries at highest risk for preventable overdose. Reducing MLIP circumvention and optimizing eligibility criteria to better capture highest risk individuals are necessary to bolster MLIP public health benefit.

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LIST OF ABBREVIATIONS

ACS	Affiliated Computer Services
ADOPT	Approaches to Drug Overdose Prevention Analytic Tool
AHRF	Area Health Resources File
APAP	Acetaminophen
AUC	Area under the curve
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
CNCP	Chronic non-cancer pain
CS	Controlled substance
CSRS	Controlled Substances Reporting System
DEA	Drug Enforcement Agency
DMA	North Carolina Division of Medical Assistance
DRIVE	North Carolina Data Retrieval Information and Validation Engine
FDA	Food and Drug Administration
FPL	Federal poverty limit
GEE	Generalized estimating equation
ICD-9	International Classification of Diseases, Ninth Revision
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
MCO	Managed care organization
MED	Morphine equivalent dose (synonymous with MME)
MLIP	Medicaid lock-in program
MME	Milligram morphine equivalents (synonymous with MED)
NC	North Carolina
NC MLIP	North Carolina Medicaid lock-in program
NPI	National Provider Identifier
NSDUH	National Survey on Drug Use and Health

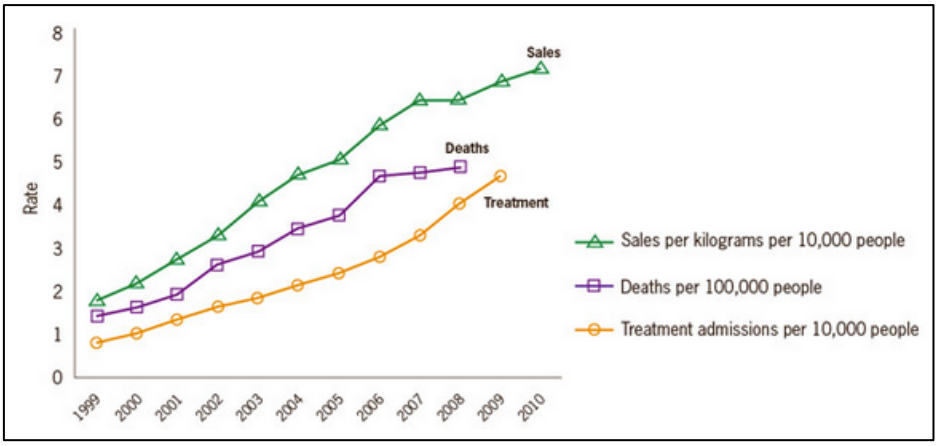
PDMP	Prescription drug monitoring program
QIC	Quasi-likelihood information criterion
RLP	Wisconsin Medicaid Recipient Lock-in Program
ROC	Receiver operating characteristic
SAMHSA	Substance Abuse and Mental Health Services Administration

CHAPTER I: INTRODUCTION

1.1 OVERVIEW

The past two decades have given rise to an epidemic of prescription drug abuse in the United States. Nearly 16 million people over the age of 12 report using a prescription medication for nonmedical (e.g. recreational) purposes in the previous year.[1] Over 10% of nonmedical users newly initiated these behaviors within the previous year. This epidemic is largely fueled by a four-fold increase in the manufacture and prescribing of controlled substance medications since 1999.[2] The drastic rise in the availability and nonmedical use of prescription drugs—particularly controlled substances—has resulted in recent alarming trends in abuse and overdose-related outcomes. Controlled substance overdose is now the second-leading cause of unintended death in the United States behind automobile accidents.[3] Between 1999 and 2008, the prescription drug overdose death rate increased 400%, reaching a peak of over 20,044 fatalities in 2008.[4] Emergency department visits related to nonmedical controlled substance use nearly tripled between 2004 and 2010.[5] Additionally, researchers estimate that nonmedical controlled substance use results in a societal economic burden of $50-$70 billion annually.[2,6] Figure 1.1 depicts the recent increases in controlled substance prescribing, overdose deaths, and healthcare utilization.[2]

Figure 1.1: Rates of opioid sales, deaths, and substance abuse treatment admissions (1999-2010)



Source: Centers for Disease Control and Prevention. Prescription painkiller overdoses in the US. November 2011; http://www.cdc.gov/vitalsigns/painkilleroverdoses/.

Much of the controlled substances used for nonmedical purposes are obtained through entirely legal prescribing and dispensing processes.[7,8] The Centers for Disease Control and Prevention (CDC) estimate that nearly 85% of abused controlled substances were originally prescribed to the nonmedical user or to a friend or relative.[1] The fact that legal distribution channels are a major source of abused medications creates an opportunity to mitigate the nonmedical use of controlled substances through policy intervention. Two of the most common policy strategies for identifying and preventing nonmedical controlled substance use occur on the state level: prescription drug monitoring programs (PDMP) and Medicaid lock-in programs (MLIP). Although the focus of this dissertation lies on evaluating the MLIP policy strategy, it is important to first understand the role of PDMPs for the purpose of establishing the current policy context in which MLIPs operate and also to lay a foundation for detailing this dissertation's novel analytic approach, which leverages the breadth of PDMP data.

PDMPs are electronic databases that automatically aggregate patient-, prescription-, prescriber-, and pharmacy-specific information for controlled substance prescriptions dispensed by community pharmacies in a state. They are currently employed in 47 states.[9] Prescribers and pharmacists can access the PDMP data to view a patient's controlled substance-seeking behaviors preceding the patient encounter in order to inform safe healthcare decisions in light of suspected nonmedical use. Currently, the primary

limitations of PDMPs include low utilization by providers and lack of interstate cooperation between state PDMP systems.[10] When accessed by providers, though, the evidence indicates that PDMPs reduce unnecessary controlled substance prescribing, prevent doctor- and pharmacy-shopping behaviors, and inform higher quality medical decision-making of controlled substance use.[11-14]

In a prior publication, I found that at least 46 states also operate MLIPs.[15] MLIPs work by, first, identifying Medicaid beneficiaries exhibiting "high risk" controlled substance-seeking behaviors.[16] Individual state MLIPs typically define high risk controlled substance use through assessment of the number controlled substance prescriptions received, as well as prescribers and pharmacies used in a given time period. Medicaid beneficiaries that exceed a state's threshold for high-risk controlled substance use based on claims review are "locked in" to specific providers—usually one prescriber and pharmacy. This means that during periods of MLIP enrollment, Medicaid will only pay for a beneficiary's controlled substance-related services if they were accessed through the designated lock-in providers.

The MLIP is intended to reduce prescription drug abuse burden in the Medicaid population by creating better care coordination among providers caring for patients with high-risk controlled substance use. Better care coordination is thought to ultimately prevent nonmedical use behaviors and adverse outcomes for the high-risk Medicaid beneficiaries enrolled in the program. Unlike PDMPs, however, the body of evidence supporting the MLIP policy strategy's public health benefit in combating nonmedical prescription drug use is minimal. There has been little to no peer-reviewed research, to date, examining the effect of MLIPs on substance abuse and overdose-related outcomes. There are also noted limitations of the MLIP intervention that may potentially undermine the current and future benefits of MLIPs in improving care coordination and outcomes from high-risk controlled substance use.

The purpose of this dissertation was to provide rigorous examination of two key MLIP limitations. The first limitation is the ability of MLIP enrollees to circumvent the lock-in provider restrictions by purchasing controlled substance prescriptions completely out of pocket. The second limitation is a stark lack of knowledge concerning measures of high risk controlled substance use that most effectively identify Medicaid beneficiaries who benefit most from MLIP intervention. To my

knowledge, findings from this dissertation represented one of the first attempts to establish an MLIP evidence base. It is hoped this new knowledge will be leveraged to inform MLIP optimizations that enhance the public health benefit of this policy strategy in fighting the prescription drug abuse epidemic.

1.2 SPECIFIC AIMS

In October 2010, North Carolina (NC) Medicaid implemented the Recipient Management Lock-In Program (further referred to as the NC MLIP). The NC MLIP enrolled beneficiaries meeting at least one of the following eligibility criteria assessed over a period of two consecutive months: ≥7 opioid prescription claims, ≥7 benzodiazepine prescription claims, and/or ≥4 unique prescribers of these medications.[17] NC MLIP enrollees were locked in to one prescriber and one pharmacy for a period of 12 months. The recent introduction of this program to the controlled substance abuse policy landscape in North Carolina—which has operated a PDMP called the Controlled Substances Reporting System (CSRS) since 2005—created a unique opportunity to contribute a rigorous MLIP examination to the peer-reviewed literature and inform state-level policy efforts to curb nonmedical prescription drug use.

The research evaluating the NC MLIP conducted herein was investigated under the umbrella of a parent project. The parent project was an interdisciplinary collaboration of researchers across the University of North Carolina at Chapel Hill. It was funded by the Centers for Disease Control and Prevention (CDC) [PI: Asheley Skinner, Grant No. CDC U01 CE002160-01]. The aims of the parent project represented initial population-level policy evaluation questions. It included a qualitative process evaluation of NC MLIP administration and quantitative investigations of the population-level effect of the NC MLIP on the number of controlled substance prescription fills and overdose events in the NC Medicaid population.

This dissertation project utilized the parent project team's rich data resources to develop research questions examining known MLIP policy limitations of MLIP circumvention and lack of consensus on optimal MLIP eligibility criteria. Specifically, this dissertation addressed the following research questions: (1) To what extent did NC MLIP enrollees adhere to program restrictions, and what patient characteristics predicted circumvention behavior? (2) Are certain opioid analgesic prescriptions more

likely to be circumvented than others? and (3) What are the most effective claims-based measures for identifying high-risk beneficiaries for potential enrollment in the MLIP?

This dissertation used a novel dataset linking Medicaid claims data with records from the North Carolina CSRS, the state's PDMP surveillance database. Because the PDMP captures data for all controlled substance prescriptions dispensed in the state regardless of payer, this merged dataset allowed observation of an MLIP enrollee's complete controlled substance-seeking behavior, whether or not they adhered to the lock-in restrictions.

The specific aims of this dissertation were:

Aim 1: To examine the effect of the NC MLIP, as well as patient-level characteristics, on controlled substance circumvention behaviors.

Controlled substance circumvention occurs when NC Medicaid beneficiaries purchase an opioid or benzodiazepine prescription entirely out of pocket without submitting a prescription claim to the Medicaid benefit. Although this behavior constitutes fraud when a Medicaid beneficiary is enrolled in the MLIP, circumvention can easily happen in situations where the MLIP enrollee visits a pharmacy and fails to inform the pharmacy of their Medicaid coverage. Also, a pharmacy may inappropriately allow the enrollee to pay the full cash price for the medication out of pocket despite knowledge of active Medicaid coverage. Circumvention of the MLIP restrictions has serious consequences for the intended public health impact of MLIPs. For MLIP enrollees that circumvent the program with the intent of abusing or diverting controlled substances, the ability to circumvent Medicaid fails to prevent access to these medications. For MLIP enrollees with legitimate medical need of controlled substances, circumvention may reflect the MLIP causing undue access barriers to necessary medications. In either case, circumvention undermines the ability of MLIPs to confer enhanced provider care coordination of these high-risk patients and it wastes state resources used to operate the MLIP.

The purpose of Aim 1 was to isolate the effect of the NC MLIP on circumvention behaviors and identify predictors of lock-in circumvention behavior in the NC MLIP population. This evidence will provide some of the first evidence of the prevalence and extent of circumvention in an MLIP population.

This will inform opportunities for targeted improvements in MLIP design and operation. Analyses for Aim 1 utilized the novel Medicaid-CSRS linked dataset. This dataset allowed identification of circumvention behavior. Circumvention was defined as the presence of an opioid or benzodiazepine prescription fill record in the CSRS dataset that lacked a corresponding prescription fill record in the Medicaid claims data. The study sample was a longitudinal cohort of adult NC MLIP enrollees with continuous NC Medicaid coverage. A retrospective cohort design with repeated monthly measures was used. We described patient-level characteristics of the study cohort and compared circumvention behavior trends across NC MLIP enrollment status through bivariate analyses. Generalized estimating equation (GEE) modeling estimated the relationship between NC MLIP enrollment, as well as select patient-level characteristics, with the likelihood and extent of circumvention at the person-month level. GEE leveraged the repeated monthly measures to account for time trends and control for within-subject correlation. The first GEE model utilized multivariable logistic regression to estimate the effect of MLIP enrollment and patient predictors on engaging in any circumvention behavior. The second GEE model examined the effect of MLIP enrollment and patient predictors on the number of circumvention fills obtained.

Aim 2: To investigate prescription-level characteristics of opioid analgesics obtained by NC MLIP enrollees through circumvention.

Aim 1 examined whether enrollment in an MLIP induced circumvention behavior and how often NC MLIP enrollees engaged in circumvention. However, this knowledge alone does not fully capture the global implications of circumvention for the public health impact of MLIPs. It is also necessary to understand the characteristics of controlled substance prescriptions MLIP enrollees obtain through circumvention. The risk of prescription overdose and mortality from nonmedical use, particularly related to opioid analgesics, is largely a function of the potency and the amount of the opioid agent ingested.[18] Higher potency opioids and larger amounts of opioids more readily contribute to adverse clinical outcomes compared to weaker opioid agents and reduced quantities. Therefore, certain opioid products used in medical practice in the United States present a greater potential for overdose outcomes. For example, opioid products classified as Schedule II agents by the Drug Enforcement Agency (DEA)

represent a group of opioids with the highest potency. Schedule II products include agents such as morphine, oxycodone, fentanyl, and methadone. Additionally, long-acting, or extended-release, opioid preparations have greater potential to contribute to overdose due to larger amounts of opioids contained within each dosing unit, as compared to short-acting products. Long-acting opioids include products such as Oxycontin tablets, transdermal fentanyl patches, and extended-release morphine capsules and tablets. Aside from Schedule II and long-acting qualities, the strength of a prescription opioid product and the prescribed quantity also play a major role in a prescription's abuse and overdose potential.

The purpose of Aim 2 was to examine the effect of NC MLIP enrollment, as well as patient predictors, on prescription-level characteristics of opioid fills received through circumvention. Specifically, three prescription-level opioid characteristics were investigated: receipt of a Schedule II product vs. non-Schedule II, receipt of a long-acting opioid vs. short-acting opioid, and the amount of opioid product received in a prescription (measured as prescribed average daily milligram morphine equivalents). Collectively, these three outcomes capture the abuse potential of individual prescriptions received by NC MLIP enrollees. Analyzing trends in these prescription-level characteristics among circumvented opioid fills provided valuable knowledge for the extent to which circumvention behavior might contribute to downstream overdose outcomes, whether NC MLIP enrollment induced changes in utilization of certain opioid products, and prescription-level characteristics that may signal attractiveness for MLIP circumventers.

Aim 2 utilized the linked Medicaid claims-CSRS dataset, as well as the same cohort of adult NC MLIP enrollees with continuous NC Medicaid coverage. A retrospective cohort study design was used for the study period of 10/1/2009 through 9/30/2012. Prescription-level characteristics of opioid fills were described and compared across MLIP enrollment status through bivariate analyses. Multivariable analyses involved a series of generalized linear models estimating the pre/post effect of NC MLIP enrollment on likelihood of receiving a Schedule II opioid, the likelihood of receiving a long-acting opioid, and differences in average daily milligram morphine equivalents prescribed. The unit of analysis was the prescription. GLM models included patient-level characteristics implemented in Aim 1. The primary

GLM analysis of these outcomes was performed in the sample of circumvented opioid fills. They were also performed in the Medicaid-covered opioid prescription fill sample and the combined sample of opioid fills from both payment sources in order to observe comprehensive trends in opioid utilization.

Aim 3: To identify and validate the most effective measures of high-risk opioid analgesic use in the NC Medicaid population.

Defining high-risk controlled substance use in the context of NC MLIP eligibility currently involves assessment of the number of controlled substance-related prescription fills and prescribers used in a given time period. However, when looking at MLIP eligibility criteria used across state Medicaid programs, there exists a remarkable lack of standardization with regard to the specific measures and thresholds used for assessing MLIP eligibility. And currently, there are no peer-reviewed studies in the literature providing evidence for the most effective strategy to define high-risk controlled substance use in the context MLIPs as it relates to notable meaningful public health outcomes.

Aim 3 analyses filled this gap in the MLIP literature by rigorously evaluating the effectiveness of various opioid exposure measures in predicting relevant clinical outcomes from high-risk opioid use. Results from this aim help establish best practices in MLIP design by informing strategies for identifying beneficiaries most likely to benefit from program enrollment from a public health perspective. Aim 3 employed a retrospective cohort design using Medicaid claims data from 10/1/2008 through 9/30/2010. The study cohort included adult NC Medicaid beneficiaries who recorded an opioid prescription claim in the first year of the study period. Survival receiver operating characteristic (ROC) modeling was employed to examine the discriminatory capability and optimal thresholds of four opioid exposure measures in predicting an outcome event during a follow-up period of up to one year. Opioid exposure measures included: number of opioid claims received, number of unique community and outpatient pharmacies used to obtain opioids, average daily opioid dose, and average daily acetaminophen (APAP) dose from opioid/APAP combination products. All opioid exposure measures were assessed over a 60-day period following the index opioid prescription fill. The primary outcome was unintentional opioid overdose, and secondary outcome measures were unintentional APAP overdose, unintentional overdose

of any drug product, diagnosed opioid use disorder, and any diagnosed substance use disorder. High performing opioid exposure measures and their optimal thresholds identified in a randomly selected testing sample were validated in the remaining subjects. Performance of optimal measures in predicting the Aim 3 outcomes was assessed through descriptive analysis, Cox proportional hazard models, and Kaplan-Meier estimation.

1.3 SIGNIFICANCE

Medicaid lock-in programs represent a highly prevalent state-level strategy for combating the ongoing epidemic of prescription drug abuse in the United States. These policies are poised to reduce nonmedical controlled substance use and its consequences among Medicaid beneficiaries—a patient population known to experience greater rates of prescription drug abuse and overdose-related death.[19-22] In fact, multiple academic and governmental sources, including the Office of the President of the United States, have explicitly identified MLIPs as a key tool moving forward in this fight.[23,24] However, rigorous evaluations of MLIPs are largely absent from the literature. Any meaningful application of MLIPs in large-scale efforts to mitigate nonmedical use will require a deep understanding of what constitutes an effective MLIP design and how lock-in enrollment impacts patient outcomes.

Findings from this dissertation project contribute significantly to this field by rigorously examining two important and previously uninvestigated MLIP limitations that may currently undermine the public health benefit of this policy. The first MLIP limitation is the problem of Medicaid circumvention. Circumvention negates the intended effect of MLIP restrictions because it reflects a failure to regulate access to inappropriate use of controlled substances and obviates the care coordination that adherence to provider lock-in restrictions would provide. From a public health perspective, circumvention is also problematic because Medicaid agencies have previously been unable to observe and respond to this phenomenon in the MLIP population. Aims 1 and 2 of this dissertation provide new and valuable knowledge to MLIP stakeholders regarding two key aspects of circumvention behavior. Aim 1 focused on characterizing the prevalence and likelihood of NC MLIP enrollees to circumvent Medicaid to obtain controlled substances. Aim 2 further rounded out our understanding of circumvention in the NC

MLIP population by investigating prescription-level characteristics of opioid analgesics obtained through circumvention. Aim 2 findings characterized whether certain opioid prescriptions were more attractive for circumvention and provided new understanding of the level of risky opioid use occurring outside the current reach of MLIP administrators. Both Aims 1 and 2 also identified patient-level predictors of their respective outcomes. This information will inform targeted MLIP design modifications and educational interventions of providers to improve adherence to MLIP restrictions and, ultimately, improve the quality of care and patient outcomes for Medicaid beneficiaries engaging in risky controlled substance use.

The second key MLIP limitation is reflected in the absence of any semblance of accepted definitions of high-risk controlled substance utilization in MLIP eligibility criteria. The findings from Aim 3 will help illuminate the most effective strategy or strategies for defining high-risk controlled substance use within the context of MLIP enrollment criteria. Validated MLIP eligibility criteria are necessary to ensure enrollment of beneficiaries most likely to benefit from this policy intervention. This information—along with lessons learned from using a novel dataset merging claims and PDMP data—will be invaluable in future efforts to create much-needed interoperable prescription drug abuse monitoring tools that aggregate multiple relevant data sources across state lines.[8,10,25-28] Lastly, the need for the evidence provided by this dissertation project concerning the effectiveness and optimal design of MLIPs is made all the more urgent by the recent and ongoing influx of millions of patients into the healthcare system as a result of expanded insurance coverage under the Affordable Care Act. Millions of newly insured Americans will gain coverage through Medicaid programs. With more Medicaid beneficiaries, MLIPs will have a greater potential impact on reducing nonmedical controlled substance use among this patient population that has borne a substantial brunt of the prescription drug abuse epidemic.

CHAPTER II: BACKGROUND, LITERATURE REVIEW, AND CONCEPTUAL MODEL

Chapter II is presented in three sections. The first section provides background information regarding controlled substance pharmaceuticals; trends in the nonmedical use of prescribed controlled substances; prescription drug monitoring program and Medicaid lock-in program policy strategies for mitigating nonmedical controlled substance use; and a description of North Carolina's PDMP and MLIP. The second section comprises a rigorous review of the literature evaluating MLIP-related outcomes and is followed by identification of gaps in the literature that motivate the research questions in Aims 1 and 2. The second section also reviews the body of evidence examining definitions of high-risk controlled substance use in prescription claims data, which provides a foundation for the investigations of Aim 3. The third section of Chapter II outlines a conceptual framework upon which analyses of the dissertation aims are based.

2.1 BACKGROUND

2.1.1 Introduction

This section details necessary background knowledge and establishes the public health and policy context in which the dissertation were developed. It provides a comprehensive overview of issues pertaining to controlled substances, including regulation, utilization trends, and the major policy strategies currently used to address nonmedical controlled substance use in the United States and in North Carolina, specifically.

2.1.2 Overview of Controlled Substances

The Controlled Substances Act of 1970 granted the Drug Enforcement Agency (DEA) and the United States Food and Drug Administration (FDA) the power to classify pharmaceuticals with no acceptable medical use or with the potential for abuse and dependency as controlled substances.[29]

Controlled substances are classified into Schedules, ranging from Schedule I to Schedule V.[30] The schedule decision is primarily informed by the degree of a drug product's abuse potential. Designation as a controlled substance imposes stricter regulations on the accessibility of these medications. For example, Schedule II prescriptions cannot have refill authorizations and must be presented to the pharmacy in a hardcopy paper form. Table 2.1 describes characteristics of each controlled substance Schedule, as well as common medication classes and products in each.

Table 2.1: Summary of federal controlled substance schedules [30,31]

Schedule	Description	Major drug classes	Primary use	Example generic drug products (Brand)
I	No accepted medical use. High abuse potential and severe psychological or physical dependence	Illicit street drugs	Recreation	Marijuana, heroin, LSD
II	High abuse potential but less than Schedule I drugs. Potential for severe psychological or physical dependence.	Opioid analgesics Stimulants	Pain ADHD	Oxycodone HCL (Oxycontin, Percocet); fentanyl (Duragesic); Amphetamine salts (Adderall); methylphenidate HCL (Ritalin)
III	Less abuse potential than Schedules I and II but more than Schedule IV. Moderate to low potential for psychological or physical dependence.	Opioid analgesics	Pain	Hydrocodone combination products (Vicodin); codeine products with <90mg/dose (Tylenol #3)
IV	Low abuse potential. Low risk of dependence.	Benzodiazepines Sedative/hypnotics Muscle relaxants	Anxiety Insomnia Muscle spasms	Alprazolam (Xanax); diazepam (Valium) Zolpidem tartrate (Ambien) Carisoprodol (Soma)
V	Lower abuse potential than Schedule IV.	Codeine-based antitussives	Cough	<200mg/mL codeine preparations (Robitussin AC)

Note: LSD=lysergic acid diethylamide; ADHD=attention deficit hyperactivity disorder; HCL=hydrochloride; mg=milligram; mL=milliliter

2.1.3 Controlled Substance Use Behaviors

The increased abuse potential of controlled substances, along with their accessibility through legal channels, makes them prime targets for undesirable medication use behaviors among patient populations and the public at large.[32] A constellation of terminology exists to describe ways in which individuals consume controlled substances outside of their intended purpose or directions for use. These include nonmedical use, misuse, abuse, dependence, addiction and pseudoaddiction.[33] Table 2.2 provides definitions for each concept, as developed by the Substance Abuse and Mental Health Services Administration (SAMHSA).

Table 2.2: Controlled substance utilization pattern definitions

Concept	Definition
Nonmedical use	Use of prescription drugs that were not prescribed by a medical professional (i.e., obtained illicitly) or use for the experience or feeling a drug causes.
Misuse	Incorrect use of a medication by patients, who may use a drug for a purpose other than that for which it was prescribed, take too little or too much of a drug, take it too often, or take it for too long
Abuse	A maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by one or more behaviorally based criteria
Dependence	Increasing tolerance for a drug, withdrawal signs and symptoms when a drug is discontinued, or the continued use of a substance to avoid withdrawal
Addiction	Increasing tolerance for a drug, withdrawal signs and symptoms when a drug is discontinued, or the continued use of a substance to avoid withdrawal
Pseudoaddiction	Drug-seeking and other behavior that is consistent with addiction but actually results from inadequate pain relief

[33]

Nonmedical use represents the broadest definition of "risky" controlled substance utilization, allowing for the fact that these substances could have been obtained through legal means or through diversion.[33] In this context, diversion means any method for distributing controlled substances, or obtaining controlled substances with the intent to distribute them, through illegal channels; this includes theft; forgery of prescriptions; receipt from friends or family members; or doctor- and pharmacy-shopping.[34] Shopping behaviors refer to visiting multiple providers to illicitly obtain large quantities of controlled substances.[35] Misuse behaviors are a subset of nonmedical use in which the medications were prescribed to the misusing individual. Abuse refers to patterns of nonmedical use or misuse that have escalated to the point of causing impairment or significant adverse health outcomes, such as overdose.[36]

2.1.4 Nonmedical Controlled Substance Use—Prevalence and Trends

Utilization of controlled substances grew exponentially in recent decades.[37-39] In fact, the manufacture and sales of opioid analgesics quadrupled from 1999 to 2010.[2] Not only did the number of prescriptions for controlled substances increase during this time compared to non-controlled medications,[40] but the average quantity of opioid analgesics per prescription rose substantially as well.[41,42] In 2012, Kenan et al's analysis of a large, nationally-representative controlled substance claims database found that the average size of oxycodone and hydrocodone prescriptions increased 69% and 67%,

respectively, between 2000 and 2010.[41] This growth has been driven in large part by a substantial, yet clinically controversial,[43,44] increase in the prescribing of opioid analgesics to treat chronic non-cancer pain (CNCP) diagnoses.[45-48] Controlled substances are now among the most commonly prescribed medications in this country; hydrocodone combination products have been the most frequently dispensed drug in the United States since the mid-2000s, with alprazolam, zolpidem, and oxycodone also ranking in the top 25.[49]

With the drastic increase in the controlled substance prescribing, it is not surprising that nonmedical use of controlled substances is highly prevalent in the United States.[50] The annual National Survey on Drug Use and Health (NSDUH), sponsored by SAMHSA, found that 6.8 million people over the age of 12 reported nonmedical use of prescription drugs in the past month—mostly involving opioid analgesics.[1] Nearly 16 million people reported nonmedical use in the past year. In addition, 750,000 Americans newly initiated nonmedical use of prescription drugs in 2012, alone. Estimates report four to six percent of adults use medications for nonmedical purposes at some point in their lifetime.[1,51-53] While the NSDUH shows relatively stable incidence of reported nonmedical use over the past decade, other evidence shows an increasing trend. In 2013, Roland, et al found that diagnosed opioid abuse doubled among privately insured patients between 2005 and 2010.[54] Research also suggests a significant shift in preference from illicit street drugs to the nonmedical use of controlled substances for recreational purposes.[55,56] A 2013 national survey reported that nearly 30% of law enforcement agencies believe controlled substances pose the greatest drug threat, up from 10% three years prior.[57]

2.1.5 Nonmedical Controlled Substance Use—Clinical Outcomes

The high prevalence of nonmedical controlled substance use translates into significant adverse health consequences—primarily overdose events and overdose-related mortality.[58-60] Overdose events involving opioid analgesics can result in death due to fatal respiratory depression, especially in the presence of other intoxicants.[61] Acute overdose of opioid/APAP combination products—as well as prolonged ingestion of greater than four grams of acetaminophen daily from these products—may also lead to death from APAP-induced liver toxicity.[62] Additionally, benzodiazepines are commonly

implicated in multi-substance overdose deaths due to its contribution to fatal respiratory depression.[63] However, acute benzodiazepine overdoses rarely cause death when they are the single intoxicant.[64] In 2008, there were over 20,000 deaths due to prescription drug overdoses in the United States; 75% of these were tied to opioid analgesics.[2,4] This represented a four-fold increase in the prescription drug overdose death rate since 1999.[4] Controlled substance overdoses are now the second-leading cause of unintended death in the United States behind motor vehicle accidents.[3]

2.1.6 Nonmedical Controlled Substance Use —Healthcare Utilization Outcomes

In addition to clinical outcomes, nonmedical controlled substance use is associated with increased utilization of costly healthcare services.[37,39,54] SAMHSA's Drug Abuse Warning Network found that, in 2011, 1.2 million emergency department visits stemmed from nonmedical prescription drug use.[5] Of these, nearly one-third were directly tied to nonmedical use of opioid analgesics and over half involved multiple pharmaceutical agents. Between 2004 and 2011, the incidence of nonmedical use-related emergency department visits increased 183%.[5] In 2011, White and colleagues found that opioid abusers were up to nine times more likely to be hospitalized, three times more likely to utilize emergency services, and they received up to four times as many prescription services compared non-abusing opioid users.[65] As previously shown in Figure 1.1, there is a striking increase in utilization of healthcare services and deaths resulting from nonmedical use observed over the past decade.[20]

2.1.7 Nonmedical Controlled Substance Use —Economic Outcomes

Not surprisingly, the dramatic rise in nonmedical controlled substance use creates substantial economic burdens on patients, payers, and society, in general.[28] It is reported that opioid abusers incur anywhere from three to seven times higher healthcare costs than non-abusers.[50,54,66,67] In 2011, White et al found that this translated to $15,000-$20,000 in excess annual healthcare costs per opioid abuser; annual out-of-pocket costs were $1,000 higher for caregivers of opioid abusers compared to those taking care of non-abusers.[65] Multiple efforts have been made in the literature recently to quantify the total societal cost of nonmedical use of controlled substances. Estimates range from roughly $25 billion in unnecessary

costs annually[68,69] up to $53 billion per year.[6] The CDC reports this figure could actually be in excess of $72 billion annually.[2]

2.1.8 Nonmedical Controlled Substance Use —Trends in North Carolina

The effects of the nonmedical controlled substance use epidemic have been felt in North Carolina, specifically. Currently, rates of controlled substance sales, reported nonmedical use, and nonmedical use-related fatalities are in line with national averages.[4,70] Most of the increase in nonmedical use fatalities were concentrated in rural Western North Carolina[71], which is consistent with other literature investigating nonmedical use trends in Appalachian regions.[72,73] Since 1997, the number of annual deaths in North Carolina due to controlled substance overdose increased around 200-300%[74,75], claiming a total of 7,100 lives by 2008.[71] Opioid analgesics and benzodiazepines were implicated in roughly 90% of these prescription overdose fatalities. Controlled substance overdoses in North Carolina were on pace to imminently (or perhaps already) surpass vehicular accidents as the leading cause of injury-related deaths in the state.[74]

2.1.9 Addressing Nonmedical Use Through Policy

Nonmedical users often obtain controlled substances through entirely legal processes involving licensed prescribers and pharmacies.[7,8,76] Results from the National Survey on Drug Use and Health found that over 80% of controlled substances used for nonmedical purposes originated as a prescription written for either the nonmedical user or one of their friends or family members.[1] Because the majority of misused and abused controlled substances are distributed through legal channels, this provides policymakers and payers with opportunities to combat nonmedical use through policy and regulatory strategies. In fact, numerous Federal entities have been on a crusade in recent years to draw attention to the epidemic of nonmedical prescription drug use. The US Department of Health and Human Services' Health People 2020 campaign explicitly identified reduction of nonmedical controlled substance use as an objective.[77] Publications from the US Government Accountability Office[28], CDC[78,79], and Centers for Medicare and Medicaid Services[80] urge policymakers and researchers to develop and implement smart policies for the identification and provision of appropriate care for nonmedical users, in addition to

infusing collaboration across local, regional, state, and Federal levels. A 2011 landmark report from the Office of the President of the United States, "Epidemic: Responding to America's Prescription Drug Abuse Crisis," recommended a four-pronged policy approach: improve patient and provider education about nonmedical use; proper medication disposal; stronger enforcement against "pill mill" prescribers; and smarter tracking and monitoring of controlled substance utilization behaviors.[23]

The attention drawn by the alarming trends of nonmedical controlled substance use in the US, coupled with the added momentum from Federal urging to address this problem, has led to many policy and practice changes in recent years. For example, many community-based organizations were created to provide direct comprehensive support and education to hard-struck areas.[81,82] Prescription drug take-back initiatives have proliferated, which remove unused or unwanted pharmaceuticals from peoples' homes that may have been misused or diverted otherwise.[83] [84,85] In clinical practice, significant efforts have been made to reduce prescription forgery[14,86], increase prescribing of abuse-deterrent opioid formulations[87], and integrate substance abuse screening instruments into regular practice.[88] Some of the most robust efforts to reduce nonmedical use of controlled substances happen through state-level policy strategies, namely prescription drug monitoring programs and, the policy strategy that is the focus of the proposed dissertation, Medicaid controlled substance lock-in programs.

2.1.10 Prescription Drug Monitoring Programs

Although this dissertation does not directly evaluate PDMPs, it is important to provide background on this strategy to fully understand the policy landscape in which MLIPs operates and to highlight how integrating PDMP and payer data—which is used for Aim 1 analyses—enhances the monitoring of risky controlled substance use.

PDMPs are electronic databases that aggregate controlled substance dispensing records in a state. They collect detailed information for controlled substance prescriptions dispensed by all community pharmacies within state lines regardless of the source of payment—out-of-pocket or payer-covered. Most states collect records for drugs in all Schedules II-V.[89] PDMPs records typically include patient-, prescription-, prescriber-, and pharmacy-level information for each prescription. Prescribers, pharmacists,

and, in some cases, law enforcement agencies, are then able to register with the PDMP and access its data through online portals to view past controlled substance utilization patterns for patients under their care. The National Alliance for Model State Drug Laws identifies five primary purposes for implementing PDMPs: "(1) to support access to legitimate medical use of controlled substances, (2) to help identify and deter or prevent drug abuse and diversion, (3) to facilitate and encourage the identification, intervention with, and treatment of persons addicted to prescription controlled substances, (4) to help inform public health initiatives through outlining of use and abuse trends, and (5) to help educate individuals about PDMPs and prescription drug use, abuse, diversion, and addiction."[89]

The concept of tracking state-level controlled substance dispensing dates back to the 1930s in California.[10] However, the introduction of two federal grant programs[90] in 2002 and 2005, as well as improved technology contributed to a recent proliferation of PDMPs. Currently, 49 states have enacted PDMP legislation and 47 operate active PDMPs.[9]

PDMPs form the cornerstone of the Office of the President's 2011 initiative to improve the tracking and monitoring of controlled substance use.[23] Despite some conflicting findings[91], the available body of evidence generally indicates that PDMPs can successfully reduce controlled substance utilization, shopping behaviors, and improve prescribing practices.[11-14,92-94] The primary limitations facing PDMPs at this date are limited provider engagement with the programs[95-97], lags in data availability, and lack of data-sharing capabilities across state lines and with other key data streams like prescription insurance claims data.[26]

2.1.10.1 North Carolina Controlled Substances Reporting System

In 2005, the state of North Carolina passed PDMP legislation establishing the CSRS, which was later implemented in 2007.[98] Prescribers and pharmacists are granted access to the CSRS, which collects records for all Schedule II through Schedule V controlled substances. CSRS data aggregates detailed patient-, prescriber-, pharmacy-, and prescription-level for each controlled substance prescription dispensed from community pharmacies within the State of North Carolina. Currently, however, the CSRS does not contain a field indicating the source of payment for the controlled substance prescription. North

Carolina pharmacies report controlled substance claims data to the CSRS weekly.[99] A recent internal evaluation of providers' experience with the CSRS found that 86% of provider respondents were registered with the program, and over 93% of providers had accessed the CSRS at least once in the previous three months.[100]

2.1.11 Medicaid Lock-In Programs

In addition to operating PDMPs, the vast majority of states (n=46) also operate controlled substance lock-in programs designed to identify, correct, and prevent high-risk nonmedical use behaviors in their Medicaid populations.[15] (Medicaid was established in 1965 by Title XIX of the Social Security Act as a joint state and federally funded health insurance program for the poor and disabled.[101]) This is not surprising given Medicaid beneficiaries are particularly susceptible to nonmedical controlled substance use behaviors and its consequences.[102] The rate of controlled substance prescribing among Medicaid beneficiaries increased two- to three-fold over the past 15 years.[19,22,48] In fact, literature has shown Medicaid beneficiaries are up to twice as likely to receive an opioid analgesic prescription than privately insured or uninsured populations, when controlling for demographic and clinical characteristics.[21,103] Notably, Washington Medicaid beneficiaries had a six-fold risk of opioid-related death, accounting for half of all such events despite making up only 22% of the state's population.[20]

MLIPs—sometimes referred to as patient review and restriction programs—attempt to mitigate these trends by enrolling beneficiaries that exhibit controlled substance utilization patterns indicative of nonmedical use. Once identified, MLIP administrators restrict their access, or "lock" them in, to specific providers as a stipulation for Medicaid coverage of controlled substance-related services. The purpose of operating an MLIP is multifactorial.[15] First, restricting beneficiaries, for example, to one prescriber and one pharmacy for their opioid prescriptions allows those providers to establish heightened levels of care coordination, deliver higher quality care, and ultimately improve health outcomes. Also, MLIPs are intended to prevent doctor- and pharmacy-shopping behaviors, which would mitigate the diversion of Medicaid-covered controlled substance prescriptions to other parties for nonmedical use. Lastly, states

stand to enjoy substantial economic savings from a reduction in unnecessary controlled substance-related services and avoidance of downstream clinical outcomes from nonmedical controlled substance use. [15]

The legal foundation for MLIPs was established in 42 CFR 431.54(e). These rules provide a general framework for MLIPs[16]:

> *(e) If a Medicaid agency finds that a recipient has utilized Medicaid services at a frequency or amount that is not medically necessary, as determined in accordance with utilization guidelines established by the State, the agency may restrict that recipient for a reasonable period of time to obtain Medicaid services from designated providers only. The agency may impose these restrictions only if the following conditions are met:*
> *(1) The agency gives the recipient notice and opportunity for a hearing (in accordance with procedures established by the agency) before imposing the restrictions.*
> *(2) The agency ensures that the recipient has reasonable access (taking into account geographic location and reasonable travel time) to Medicaid services of adequate quality.*
> *(3) The restrictions do not apply to emergency services furnished to the recipient.*

The Federal rules only stipulate that MLIPs must inform candidates of the lock-in decision prior to their MLIP enrollment, must ensure reasonable access to quality Medicaid services, and must not impede access to emergency medical services. The rest of the program design decisions are left up to state Medicaid agencies. These decisions include the MLIP enrollment criteria, qualifying medication classes, which provider(s) MLIP enrollees get locked in to, and the duration of the lock-in period. Most MLIPs restrict enrollees to either one pharmacy or one pharmacy plus one prescriber. The lock-in period typically lasts from 12 to 24 months, with some states employing longer subsequent lock-in periods if the nonmedical use behaviors do not resolve after the initial enrollment term. In addition, most states define their MLIP eligibility criteria using threshold measures of numbers of controlled substance prescription claims and number of controlled substance prescribers and pharmacies used. However, considerable variability exists in how state MLIP administrators utilize these measures to define their criteria for "excessive" use of controlled substance services (Table 2.3).[15]

Table 2.3: Enrollment criteria for states with publicly available Medicaid lock-in eligibility details (as of 2/22/14)[a]

State	Assessment period[b]	Prescription criteria	Prescriber criteria	Pharmacy criteria	Other criteria
Alaska	Monthly for 2 consecutive months	Receipt of prescriptions with frequency ≥2 standard deviations of mean; Receipt of prescriptions from ≥1 prescribers in total average daily doses exceeding those recommended in *Facts & Comparisons*			Provider referral
Colorado	3 months	≥3 drugs in the same therapeutic category; ≥16 prescriptions		≥3 pharmacies	Provider referral
Idaho	60 days	≥6 benzodiazepine claims; ≥8 opiate claims; ≥3 tramadol claims; ≥480 tramadol tablets; ≥6 months of continuous muscle relaxant use	Use of "multiple" prescribers	Use of "multiple" pharmacies	"Excessive" ED use; Drug dependence or abuse history; Provider referral
Kentucky	2 consecutive 180-day periods	≥10 different prescription drugs;	≥5 prescribers	≥3 pharmacies	≥4 ED visits for non-emergency; ≥3 different EDs used for non-emergency
Massachusetts	3 months	≥11 Schedule II-IV prescription fills; AND	≥4 prescribers; OR	≥4 pharmacies	
Michigan	3 months	≥5 claims for CS or muscle relaxants; "Aberrant" CS utilization patterns over 1 year	≥2 prescribers for duplicate services	≥3 pharmacies	≥3 ED visits; Repeat ED use with no follow-up; Repeat ED use for non-emergency
Nevada	60 days	≥9 CS claims			
New Hampshire (any three criteria)	90 days	≥3 drugs in same drug class; Same/similar drug received from different pharmacies within 2 days; 100 units per prescription per 7-day supply	≥3 prescribers	≥3 pharmacies	≥2 ED visits
New Jersey	NR	≥2 prescription fills "in excess of what any one prescriber would intend"	Use of "multiple" prescribers	Use of "multiple" pharmacies	Presentation of forged or altered prescription
North Carolina	2 consecutive months	≥6 benzodiazepine claims; ≥6 opiate claims	≥3 prescribers		Provider referral
Oregon	6 months	“Exhibit patterns of drug misuse”	Use of "multiple" prescribers to obtain same/similar drugs	≥3 pharmacies	

Utah	12 months	≥6 CS prescription fills[c]	≥3 prescribers	≥4 pharmacies	≥4 primary care providers visited; ≥4 specialists visited; ≥5 ED visits for non-emergency
Virginia	3 months	Exceed 200% max therapeutic dose of drug class or 100% max therapeutic dose of drug class from ≥2 prescribers for period ≥4 weeks; Duplicate prescription fills within 2 days on two separate occasions; ≥2 CS prescriptions from ≥2 pharmacies or ≥2 prescribers for period ≥4 weeks; ≥24 prescriptions; ≥12 CS prescriptions	≥3 prescribers; ≥2 physician visits for similar diagnoses within 2 days	≥3 pharmacies	≥3 ED visits for non-emergency; Provider referral; Pattern of non-compliance
Washington (any two criteria)	3 months	≥10 prescriptions; CS prescriptions from ≥2 prescribers (automatic eligibility if this criterion met)	≥4 prescribers	≥4 pharmacies	Similar services from ≥2 providers on same day; ≥10 office visits; ≥2 ED visits (automatic eligibility); "At risk" fraudulent behavior (automatic eligibility)
West Virginia	60 days	Suboxone therapy in last 30 days; ≥6 claims within single class with abuse potential; ≥6 claims from ≥3 classes with abuse potential; ≥16 claims for all drugs with abuse potential; "Doctor shopping" involving ≥6 claims for drug with abuse potential from ≥3 prescribers filled at ≥2 pharmacies	≥3 prescribers of drugs with abuse potential		History of dependence; History of poisoning/overdose
Wyoming	NR		≥2 prescribers	≥2 pharmacies	

Note: CS=controlled substance; ED=emergency department; NR=not reported. Information in this table reflects evidence identified in published literature and publicly available sources online.

a. Eligibility for lock-in enrollment contingent on meeting one individual criterion listed within the state, except where noted as otherwise.

b. Assessment of individual lock-in enrollment criteria occurs over the designated time period in this column, except where noted with criterion as otherwise.

c. CS utilization criteria for Utah Medicaid Restriction Program assessed over time period shorter than 12 months, but exact duration unavailable

Table from: Roberts AW, Skinner AC. Assessing the Present State and Potential of Medicaid Controlled Substance Lock-In Programs. *J Manag Care Pharm.* May 2014;20(5):439-446c.

Unlike the PDMP policy strategy, there is limited peer-reviewed evidence available to inform our current understanding of optimal MLIP design and the effectiveness of MLIPs in achieving positive effects on nonmedical controlled substance use. Available literature pertaining to MLIP-related outcomes and MLIP enrollment criteria design are discussed in Sections 2.2 and 2.3, respectively.

2.1.11.1 North Carolina Medicaid Recipient Management Lock-In Program

North Carolina Medicaid implemented their MLIP, the Recipient Management Lock-In Program, in October of 2010.[17,104] North Carolina Medicaid beneficiaries are eligible for MLIP enrollment if they meet at least one of the following criteria based on retrospective utilization review of NC Medicaid claims data and are not being treated for cancer:

- Fill ≥7 opioid analgesic prescriptions in a period of two consecutive months;
- Fill ≥7 benzodiazepine prescriptions in a period of two consecutive months;
- Receive opioid or benzodiazepine prescriptions from four or more unique prescribers in a period of two consecutive months;
- Referred for enrollment from a provider or the North Carolina Division of Medical Assistance.

The North Carolina Division of Medical Assistance (DMA) administers the NC MLIP but contracts with a third-party vendor, Affiliated Computer Services (ACS), to manage program enrollment. ACS retrospectively applies the NC MLIP enrollment criteria to the most recent 60 days of Medicaid claims data to identify beneficiaries eligible for lock-in. Roughly 3,000 to 4,000 Medicaid beneficiaries meet the inclusion criteria at any given time.[105] They then rank those eligible for the MLIP by severity of controlled substance seeking-behavior, which is assessed through clinical pharmacist review and a proprietary algorithm that considers number of prescriptions received, providers used, and controlled substance costs incurred. ACS then provides DMA with the prioritized list of eligible Medicaid beneficiaries, at which point DMA conducts another clinical drug utilization review and begins the MLIP enrollment process for the finalized list of eligible individuals.

MLIP enrollees are notified of their lock-in status through a mailed letter and have a 30-day period in which to designate one preferred lock-in pharmacy and one preferred lock-in prescriber. Once enrolled, individuals are locked in to their preferred prescriber and one pharmacy—or assigned a

prescriber and pharmacy if no preference is designated—for North Carolina Medicaid coverage of services involving benzodiazepine and opioid analgesic medications. The initial enrollment period lasts 12 months, at which point enrollees are evaluated for release from the MLIP or for re-enrollment.

DMA phased in NC MLIP implementation by enrolling roughly 200 eligible NC Medicaid beneficiaries into the MLIP each month beginning in October 2010. For example, in the first six months of MLIP implementation, the number of lock-in beneficiaries increased from 58 to 954.[105]

2.2 LITERATURE REVIEW—MLIP Outcomes and Evaluations

2.2.1 Section Overview

Despite the majority of state Medicaid agencies operating controlled substance lock-in programs, relatively little is known about the effectiveness of this policy strategy in mitigating the nonmedical use of prescribed controlled substances or its effect on a broad range of utilization, economic, and clinical outcomes. This section provides a comprehensive review of all available evidence for the effects of Medicaid lock-in programs. In sections 2.2.2 through 2.2.4, we summarize the landscape of evidence for the effect of MLIP policies on general economic, utilization, and clinical outcomes found in the peer-reviewed literature, two doctoral dissertations, and unpublished MLIP grey literature. We utilized PubMed, Google Scholar, and Web of Science databases to conduct the review of relevant published literature prior to May 2014. We searched the grey literature using Google, Google Scholar, and comprehensive review of individual state Medicaid agency websites prior to May 2015. This non-published evidence was largely comprised of publicly accessible reports and presentations developed from internal MLIP administrator evaluations. For both the published and grey literature searches we used free-text and Boolean operator strategies with key search terms, such as “Medicaid,” “controlled substance,” “lock in,” “restriction,” “recipient management,” and individual state names and state MLIP monikers. We also identified relevant sources of evidence through secondary review of article bibliographies to ensure complete capture of evidence.

Then in sections 2.2.5 and 2.2.6, we explicitly discuss the limited available evidence for the effect of MLIPs on circumvention behavior outcomes, which are the specific MLIP outcomes investigated in Aims 1 and 2, respectively. Section 2.2 closes with a summary of the body of MLIP outcomes evidence and identification of major gaps in the literature that informed the development of the research questions posed in both the parent project and Aims 1 and 2 of this dissertation.

2.2.2 General MLIP Outcomes—Peer-Reviewed Literature

The first MLIP evaluation was conducted in Missouri by Singleton in 1971, the year after its implementation.[106] At the time, Missouri Medicaid beneficiaries were identified for MLIP enrollment through a combined automated and manual patient review focusing on aberrant shopping behaviors and excessive quantities of prescriptions received. Missouri MLIP enrollment reached nearly 6,000 beneficiaries per quarter in 1970. Singleton only analyzed economic outcomes among this sample, but he estimated the MLIP would result in nearly $11 million in savings to the state annually.

Another early MLIP evaluation was conducted in Hawaii's Medicaid program in 1984 by Chinn.[107] Hawaii's MLIP restricted enrollees to any combination of a primary care physician, pharmacy, clinic group, or hospital. Beneficiaries qualified for MLIP enrollment by displaying aberrant prescriber, pharmacy, or controlled substance use. Chinn identified 270 individuals enrolled in Hawaii's MLIP between July 1977 and December 1983. Fifty (21%) of the enrollees were found to be compliant with the MLIP restrictions for 12 months following enrollment, as identified by "fair hearings" taking place between MLIP administrators and enrollees. Fair hearings with all 270 enrollees identified "very few" beneficiaries that continued pre-enrollment levels of Medicaid services abuse. Chinn also estimated that the MLIP resulted in $909,922 in total savings to the state for the year of 1983, alone.

A 1998 peer-reviewed presentation abstract from Blake et al. described the results of an investigation into the Louisiana Medicaid lock-in program's effect on pharmacy provider continuity, prescription utilization, and prescription expenditures. The authors performed a pre-post examination of a retrospective cohort of 1,490 Louisiana Medicaid lock-in enrollees using segmented regression analyses to analyze trends following MLIP implementation.[108] The authors found a significant increase in the total

number of prescriptions filled at a single pharmacy following enrollment in the MLIP. The total number of unique drug products received per enrollee, utilization of Schedule II narcotics, and total prescription expenditures all decreased significantly following MLIP enrollment. Further unpublished findings related to Blake's analyses are reported in Section 2.2.3 below.

Hladilek and colleagues conducted a broad overview of quality initiatives employed in the Wisconsin fee-for-service Medicaid population in 2004.[109] One such quality initiative they studied was the Recipient Lock-In Program (RLP), which was implemented six years prior and had an enrollment of 62 to 250 beneficiaries over that time. Although their evaluation primarily focused on the efficiency of communicating notices of beneficiary qualification for RLP enrollment to providers and patients, they also looked at utilization and economic outcomes. Their analyses, which were based on 1997 data, found that RLP enrollment was associated with a 24% decrease in prescription expenditures and similar decrease in emergency room visits and inpatient hospitalizations. A cost benefit analysis found that for each dollar invested in administering the RLP, the state saved $6.16, which validated a prior return-on-investment analysis.[110]

Oklahoma Medicaid administrators also published a summary of results of an evaluation of their Pharmacy Lock-In Program in a 2009 issue of the *Journal of the Oklahoma State Medical Association.*[111] The article states that lock-in enrollment significantly improved healthcare-seeking behaviors of Medicaid beneficiaries, including narcotic medication use, doctor- and pharmacy-shopping behaviors, and emergency department use. The average number of monthly narcotic claims per Oklahoma Medicaid member steadily decreased from 2.5 immediately preceding MLIP implementation to slightly over one fill per month one year following the program start date. Further unpublished results from this evaluation are detailed in Section 2.2.4.

The most recent peer-reviewed published data regarding MLIP-related outcomes comes from a paper presented by Kachur, et al., at the 2013 AcademyHealth Annual Research Meeting.[112] The authors identified 111 adult beneficiaries of the Medicaid Managed Care Organization (MCO) in Maryland initially enrolled in the state's MLIP between March 2008 and February 2011. MLIP enrollees were

locked in to a single prescriber and pharmacy. The authors utilized a comparator group of 2,248 Medicaid MCO beneficiaries not enrolled in the MLIP but were identified as exhibiting opioid overuse by the health plan. The Medicaid MCO defined overuse as eight or more opiate prescriptions written by three or more prescribers during the previous six months. The authors used bivariate analyses to investigate demographic and disease burden differences between groups, and retrospective difference-in-difference methods were used to estimate the differential effect of MLIP enrollment on opiate utilization and healthcare utilization between study groups for six-month periods prior to and following enrollment.

MLIP enrollees were slightly younger at 37.4 years of age, on average, compared to 42.1 years for the non-MLIP beneficiaries.[112] Both groups were roughly 70% female. MLIP enrollees were more likely to reside in suburban (44.1%) and urban settings (34.2%), as opposed to the comparator group, of which 40% lived in rural settings. Disease burden was similar between the groups, with about 30% of each sample having at least five diagnosed chronic conditions. Following MLIP enrollment, study subjects displayed a significant decrease in mean number of opiate prescribers (2.29 vs. 0.85), mean number of opiate prescriptions (3.18 vs. 1.53), and per-member-per-month opiate costs ($157 vs. $153). Difference-in-difference analyses indicated these differences remained significant when considering comparison group trends. Kachur and colleagues also found significant decreases in utilization of primary care providers and emergency care, as well as total healthcare expenditures. However, these were insignificant in difference-in-difference analyses. MLIP enrollment had no impact on receipt of substance abuse treatment services.

2.2.3 General MLIP Outcomes—Doctoral Dissertation Findings

Two doctoral dissertations evaluating Medicaid lock-in programs were identified in the ProQuest Dissertations & Theses Full Text database.[113]

In 1997, Blake completed a comprehensive evaluation of Louisiana Medicaid's lock-in program.[114] This investigation included 1,490 MLIP enrollees and assessed utilization and economic outcomes for the 12-month periods before and after enrollment in the MLIP. Study subjects were 48 years of age, on average, and mostly female, White, and residing in metropolitan areas. Louisiana MLIP

enrollees also had poor health status. Three-fourths of the study sample received Supplemental Security Income disability benefits. The mean number of comorbidities per enrollee was 24.5, defined as unique five-digit International classification of Diseases, Ninth Revision (ICD-9) diagnosis codes during the pre-enrollment period.

Major findings from Blake's dissertation work were previously discussed in Section 2.2.2 with regard to the conference presentation abstract published by Blake, et. al.[108] In short, using an interrupted time series design, Blake found the Louisiana MLIP reduced polypharmacy, Schedule II narcotic prescription fills, inpatient days, physician office visits, diagnostic tests, pharmacy costs, and total healthcare costs. The program also improved provider continuity, with the number of enrollees using a single physician increasing from 52% in the pre-MLIP period to 83% in the post-MLIP period and use of a single pharmacy increasing from 63% to 92%.

Beaubien completed dissertation work in 2005 that examined of the effect of a Northeastern Medicaid managed care organization lock-in program on pharmacy and healthcare utilization.[115] This portion of the project identified a retrospective cohort of 307 Medicaid MCO beneficiaries enrolled in the MLIP in the calendar year of 2001. Similar to previously discussed studies, the Northeastern MLIP enrollees were predominantly female with a mean age of 44 years. Beaubien employed a pre-post design using enrollees' pharmacy and medical claims data available for one year periods prior to and following lock-in enrollment. The MLIP was associated with a 17% reduction in controlled substance prescription claims. The number of medical claims from both outpatient office visits and emergency department visits were consistent before and after MLIP enrollment. The number of medical claims originating from an inpatient hospital setting increased 16% following MLIP enrollment. Beaubien partially attributes the observed trends partially, however, to underlying historical trends seen in the general Medicaid population.

2.2.4 General MLIP Outcomes—Unpublished MLIP Evaluation Data

Multiple sources of MLIP evaluation data were identified through comprehensive search of the grey literature. Most of these sources took the form of commissioned reports or presentation materials that

communicate results from internal state MLIP evaluations. First, a recent evaluation of the North Carolina Medicaid Recipient Management Lock-In Program is highlighted. Then, additional unpublished MLIP evidence is reported, grouped by economic, utilization, and clinical MLIP outcomes.

2.2.4.1 General MLIP Outcomes—Internal North Carolina MLIP Report

The State of North Carolina commissioned a report in 2011 to evaluate the impact of their MLIP, implemented in October 2010, on healthcare utilization and outpatient pharmacy costs.[105] The evaluation assessed changes in outcome measures between the six month period before the MLIP start date—April through September 2010—and the six month period following—October 2010 through March 2011. Because enrollment of qualifying beneficiaries into the MLIP was steadily phased in at a rate of roughly 200 additional enrollees monthly, this evaluation captured a total of 2,909 person-months of exposure to the MLIP policy. They also utilized a comparator group of beneficiaries meeting the state's criteria for MLIP enrollment but were not yet enrolled into the program during the study period.

The report estimated the MLIP was associated with $279,500 in total gross outpatient pharmacy savings in the first six months of MLIP implementation.[105] Fourteen percent of MLIP enrollees incurred no pharmacy costs to North Carolina Medicaid following their lock-in, which accounted for almost 40% of the estimated savings. (The authors do not speculate about the lack of subject observation in Medicaid claims data following lock-in, but this finding could indicate circumvention behaviors that will be investigated in Aims 1 and 2of this dissertation). A total of 55% of the estimated $279,500 in total pharmacy savings were attributed to reduced claims for MLIP qualifying medications, including opioid analgesics and benzodiazepines. The MLIP resulted in a mean reduction of 2.8 total prescription claims per enrollee and a mean reduction in controlled substance claims per enrollee of 2.0 fills. Utilization of inpatient, outpatient, emergency, and radiology services were unchanged among MLIP enrollees during the post-implementation period. Subsequent internal evaluations found that 2.3 million fewer opioid analgesic tablets were dispensed in the first three months of MLIP implementation, with a total of $5.2 million in savings to the state in its first year.[116]

2.2.4.2 General MLIP Outcomes—Unpublished Economic Findings

Much of the grey literature—and for that matter, peer-reviewed literature—focus on MLIPs' economic impact on state expenditures. The State of Washington conducted two large-scale evaluations of its MLIP; one in 2005 that assessed the first three years of the program's operations when enrollment increased from 200 to 3,000 beneficiaries[117] and again in 2012 with a cost-effectiveness analysis when enrollment topped out at 3,800 individuals.[118] The state studied a nine month pre-MLIP and six month post-MLIP observation period and reported monthly savings of $1.5 million due to its MLIP[117], with a return on investment of $6.61 for each dollar spent administering the MLIP. [118]

In addition, presentation materials from Best and colleagues also describe findings from an unpublished randomized controlled trial that was conducted in 2008 and included economic outcomes.[118] The study assigned 503 qualifying Washington Medicaid beneficiaries to MLIP enrollment and 188 beneficiaries meeting enrollment criteria to an observation-only control group.[118] The researchers employed a difference-in-difference intention to treat analysis looking at changes in outcomes between pre- and post-enrollment observation periods of 12 months. Enrollment in the Washington MLIP was associated with significant decreases in physician, emergency care, planned hospitalization, and total Medicaid costs. No difference was found between MLIP and control groups in total pharmacy costs.

Many other states reported economic savings in internal MLIP evaluations. In 2012, Keast presented results of a pre-post MLIP enrollment analysis among 52 Oklahoma Medicaid beneficiaries who were locked in to a single pharmacy.[119] This investigation found significant decreases in pharmacy- and emergency department-related costs. A 1995 audit of Utah's MLIP found a decrease in total healthcare costs of 50% for their 22 enrollees. Kentucky MLIP administrators forecasted savings to the state of over $6,300 per lock-in enrollee.[120] Iowa Medicaid's lock-in program saved the state $2 million annually.[121] Florida's MLIP saved the state nearly $13 million over the programs first three years.[122] Similar economic findings are available for Connecticut[123,124], Illinois[125], Massachusetts[126], South Carolina[127], and West Virginia[128].

2.2.4.3 General MLIP Outcomes—Unpublished Utilization Findings

In addition to economic outcomes from MLIPs, much of the unpublished MLIP evidence centers on healthcare utilization measures. And similar to the unpublished economic findings, MLIPs generally resulted in significant decreases in utilization of Medicaid services.

In the 2005 report from the State of Washington, the average number of narcotic prescription claims per enrollee lowered from 3.1 to 1.6, the total dosage of opioid analgesics received by enrollees decreased over 40%, and the average number of prescribers per person reduced from 4.8 to 2.8 following lock-in.[117] In 2012, the State of Washington found that, in the six months following an expansion of the MLIP, lock-in enrollees exhibited a 37%, 33%, and 24% decrease in outpatient care, emergency care, and prescription utilization, respectively.[118] Best and colleagues also reported significant decreases in physician visits, emergency care visits, planned hospitalization costs, total narcotic prescription claims, and total narcotic tablets dispensed in the MLIP arm of their unpublished 2008 randomized controlled trial. No significant changes were found for total hospitalizations.

Utilization outcomes from the 2012 Oklahoma MLIP evaluation included significant decreases in total prescription claims, narcotic prescription claims, number of pharmacies used, number of prescribers used, and emergency department visits.[119] Interrupted time series analysis showed that the MLIP enrollment not only caused a reduction in the level of average monthly narcotic prescription claims per enrollee, but it also caused the trend line to flip from an upward trend of 0.05 fills per month prior to lock-in to a downward trend of -0.04 fills per month.

Lastly, an early internal Utah MLIP evaluation conducted in 1995 reported significant decreases in emergency room visits, multiple pharmacy use, and narcotic prescription claims in the magnitude of 65-75%.[129]

2.2.4.4 General MLIP Outcomes—Unpublished Clinical Findings

Only one unpublished source of MLIP outcomes evidence—the 2012 presentation materials from Best and colleagues in Washington State—investigated any type of clinical outcomes from MLIP enrollment. They reported that the 2008 randomized controlled trial, which investigated 12-month

outcomes among roughly 500 MLIP enrollees and 200 assigned to observation only, found no significant changes in all-cause mortality between the MLIP intervention and control groups.[118]

2.2.5 Aim 1 MLIP Outcome—Engaging in Lock-in Circumvention

The potential for circumventing Medicaid and its MLIP restrictions remains one of the most notable limitations of the lock-in policy strategy.[130] Circumvention occurs when Medicaid beneficiaries obtain controlled substances through cash purchases of these prescriptions, unbeknownst to the Medicaid program. In the context of MLIP enrollees, circumvention results in wasted MLIP resources. It represents a failure to prevent risky controlled substance utilization and to confer enhanced provider coordination of healthcare delivery. Very little attention has been paid to investigating the prevalence, patterns, and predictors of circumvention behaviors in MLIP programs. Only in the past two years have researchers begun to recognize the need to examine circumvention behaviors to assess its impact on the effectiveness of MLIPs as a policy tool in preventing controlled substance abuse and misuse.[119]

First, in Kachur et al.'s 2013 published abstract, the authors explicitly recommend researchers investigate the prevalence and predictors of circumvention in MLIP populations.[112] In addition, the 2012 presentation materials from Best and colleagues briefly mentions Washington Medicaid's recent efforts to link their Medicaid claims database with data from the state's prescription drug monitoring program.[118] This dataset allowed for identification of lock-in circumvention behaviors not observable in the Medicaid claims alone, similar to the dataset used in Aim 1 and 2 analyses. No peer-reviewed investigations into compliance with the MLIP restrictions have been published using Washington's merged dataset, to date. However, their initial explorative analyses found over 2,000 clients in 2012—representing over half of their MLIP enrollees—had cash and Medicaid paid schedule prescriptions on the same day and have "identified 478 clients in 2012 where cash and Medicaid fills were <10 days apart and for the same drug and with a different prescriber."

Despite Best's presentation and Kachur's abstract being the only known sources recognizing circumvention outcomes in MLIPs, it is possible that the existing literature reporting reductions in the number of controlled substance prescription fills due to MLIPs may have unknowingly captured

artifactual evidence of circumvention in MLIPs. For example, the unpublished evaluation of Oklahoma's MLIP reported a reduction in monthly narcotic prescription fills among program enrollees.[119] It is possible that this finding is partially attributable to Oklahoma MLIP enrollment inducing enrollees to engage in circumvention behaviors. Because narcotic prescriptions obtained through circumvention would not appear in the Oklahoma Medicaid claims data, highly prevalent circumvention behaviors would make it appear as though the lock-in program had an artificially exaggerated effect on reducing narcotic prescription use in the Medicaid data.

The lack of interest in circumvention behaviors in Medicaid lock-in programs shown in the published and unpublished literature prior to 2012 may be due to the recent momentum behind mitigating the public health epidemic of prescription drug abuse. States may have previously viewed MLIPs primarily as a tool for reducing expenditures, in which addressing circumvention behaviors was a low priority. After all, Medicaid agencies do not pay for circumvented controlled substance prescriptions. Now, the recent preliminary circumvention findings from Best and colleagues—in addition to a strong recommendation to examine MLIP circumvention behaviors by Kachur—may signal a shift in perception of MLIPs from strictly a cost savings and punitive measure to a tool for improving public health, in which preventing circumvention would be of high priority to ensure optimal program effects.[112]

This provides clear motivation for conducting the analyses in Aims 1 and 2 of this dissertation. Findings from Aim 1 will isolate the effect of enrollment in the NC MLIP on the likelihood of engaging in circumvention and identify patient-level predictors of obtaining controlled substances through circumvention within the NC MLIP population. Aim 2 will characterize the riskiness of opioid use occurring through circumvention by describing prescription-level opioid potency and dosage characteristics obtained across payment sources. Aim 2 will also examine the effect of MLIP enrollment and patient predictors on use patterns of these prescription-level characteristics.

2.2.6 Aim 2 MLIP Outcomes—High-Risk Opioid Prescription Use

Aim 1 of this dissertation addresses the lack of knowledge regarding whether, and to what extent, MLIP enrollment causes people to circumvent Medicaid for controlled substance prescriptions. While it is

necessary to understand *how often* circumvention occurs in MLIPs, it is also crucial to understand *which* controlled substance prescriptions are being circumvented. Without knowledge the abuse/overdose potential of individual prescriptions obtained through circumvention, it is not possible to fully gauge the extent to which MLIP circumvention behavior counteracts the program's intended reduction of high-risk utilization behavior. Aim 2 addresses this other key aspect of MLIP circumvention behavior by investigating prescription-level characteristics of circumvented opioid analgesic prescription fills in the NC MLIP. The specific prescription-level markers of interest were Schedule II classification, long-acting opioid formulation, and prescribed daily opioid dose. These three outcomes were selected for their representation of opioid potency and level of opioid exposure, which are key factors in the physiological process of developing dependence or experiencing overdose. They are also known markers of highly sought opioid prescriptions among abusers.

Schedule II opioid products are those deemed by the DEA to have the highest potential for abuse.[30] Their high potential for abuse stems from pharmacological properties, namely high potency, that more readily lead to psychological dependence, physical dependence, and euphoric effects for the user.[18] Commonly used Schedule II opioid products during the dissertation study period included oxycodone, morphine, fentanyl, methadone, hydromorphone, oxymorphone, and tapentadol. Prior literature has shown receipt of Schedule II opioids as having strong association with abuse-motivated controlled substance use behavior. In 2013, Cepeda and colleagues conducted a retrospective cohort study of over 25 million opioid users in the United States and found that most (nearly 70%) opioid users exhibiting doctor-shopping behavior sought Schedule II products.[131] A 2014 study of the California PDMP data reported that opioid doctor-shoppers received up to six-times higher cumulative amounts of Schedule II opioid products than opioid users who didn't exhibit abuse-motivated behavior.[132] Another large retrospective cohort study found 40% higher odds of abuse behaviors among Schedule II opioid users, controlling for numerous patient-level confounders.[133] Schedule II opioid use was also a primary outcome of Blake's study of the effect of Louisiana's MLIP on high-risk controlled substance use behaviors.[108,114]

Long-acting opioid products present an increased risk of opioid abuse and overdose outcomes for two primary reasons. First, long-acting opioid products typically contain high potency opioid agents. Second, long-acting opioid products contain high quantities of opioids within each dosage form, because they are designed to release medication for sustained periods of time. Commonly used long-acting opioid products at the time of the dissertation study period included transdermal preparations of fentanyl and buprenorphine and extended-release oral formulations of oxycodone, morphine, methadone, tapentadol, oxymorphone, and hydromorphone. Similar to the evidence for Schedule II products, prior literature has demonstrated significant concern for the role of long-acting opioid preparations in contributing to abuse and overdose. A 2012 study of a Washington State worker's compensation system opioid overdose-prevention policy was primarily focused on the policy's effect on unsafe prescribing of long-acting opioid products.[134] Long-acting opioid use was also a key predictor throughout the TROUP investigations of opioid abuse outcomes in a private payer and Medicaid sample.[133,135-137] One of these studies found over 2.5 times increased risk of an overdose event among long-acting opioid users compared to those only using short-acting opioids.[135] A nearly identical result was found in a recent study of a large retrospective cohort of United States Veterans.[138]

The average prescribed daily dose of opioids—assessed as mean milligram morphine equivalents per day—has become a gold standard measure of prescription-level risk of opioid abuse and overdose. The average daily MME measures total opioid exposure by accounting for the potency of the opioid agent, prescribed drug strength, quantity, and dosing instructions within a single measure. A substantial body of evidence has developed over the last decade for the utility of the average MME in predicting a person's risk for opioid abuse and overdose.[139] Notably, the TROUP investigations and other landmark studies have demonstrated a clear trend of increased average daily prescribed MMEs being associated with significantly increased risk of opioid abuse and overdose events.[131,133,135,137,140-144] Best also employed average MME/day as a key outcome in the investigation of Washington State's MLIP in 2012.[118]

Taken as a whole, these three prescription-level opioid characteristics capture a prescription's potential for contributing to adverse outcomes from high-risk opioid use behaviors. They also represent an opioid prescription's attractiveness to MLIP enrollees intent on abusing or diverting these medications. Prescriptions for high potency opioids and high quantities of opioids are targeted by individuals engaged in high-risk behaviors, such as doctor and pharmacy shopping.[37,131,145] In fact, prescription opioid abusers enrolled in a 2009 focus group study explicitly indicated that high potency opioid agents, high quantities of opioids, and long-acting opioid products were the most appealing for abuse and diversion.[146]

There are two primary motivations in Aim 2 for examining trends in these opioid prescription-level characteristics in the context of NC MLIP circumvention. First, describing the types of opioid prescriptions that MLIP enrollees obtain through circumvention, when coupled with information about the extent of circumvention events from Aim 1, provides new evidence for the cumulative level of opioid exposure occurring beyond the reach of MLIP administrators. By extension, this allows assessment of the effect of MLIP enrollment on comprehensive exposure to opioids among NC MLIP enrollees from all payment sources. Second, Aim 2 provides evidence for the effect of NC MLIP enrollment, and patient predictors, on the likelihood of circumventing opioid prescriptions with high-risk attributes. It is widely regarded by Medicaid agencies that the controlled substance-seeking behaviors leading to MLIP eligibility often reflect intent to abuse these medications or divert them to third parties.[130,147-149] Medicaid circumvention presents a viable route for MLIP enrollees to engage in abuse-motivated controlled substance use behaviors largely unchecked. Recent attention to the issue of MLIP circumvention[112,118,130], coupled with MLIP enrollees' heightened awareness of their Medicaid service use being monitored, raises concerns that MLIP enrollment may actually induce high-risk opioid use behaviors occurring outside the purview of Medicaid among enrollees highly motivated by abuse. Therefore, it is necessary to examine if MLIP enrollment results in increased circumvention of high-risk prescriptions and whether certain prescriptions have increased attractiveness for circumvention in order to inform improvements to the MLIP policy intervention.

2.2.7 MLIP Outcomes—Summary and Gaps

Section 2.2 describes findings from all available evidence for the effect of Medicaid lock-in programs on economic, utilization, and clinical outcomes. This review of the peer-reviewed and grey literature established our current understanding of MLIP effectiveness and provides motivation for the aims of this dissertation's parent project—which involved a population-level policy analysis of controlled substance utilization and overdose outcomes—as well as Aims 1 and 2 of this dissertation, which investigated potential unintended consequences of MLIP enrollment in the form of lock-in circumvention behaviors. In general, minimal evidence exists to understand the public health benefit of MLIPs in reducing prescription drug abuse behaviors and outcomes.

Review of the literature identified six total peer-reviewed publications investigating Medicaid lock-in program-related outcomes. Two of these studies were published over 30 years ago.[106,107] Two more publications from the previous decade provided evidence for state economic savings from MLIPs as well as positive impacts on use of Medicaid healthcare and prescription services.[109,111] However, these articles were short, cursory programmatic evaluations with a narrow focus on the budgetary impact of MLIPs. The remaining peer-reviewed evidence consisted of conference poster presentations with a similar focus on economic and utilization outcomes.[108,112] The breadth of evidence from these published presentation abstracts was limited, however.

Thorough review of the grey literature found that the vast majority of available MLIP evaluation data comes from publicly accessible, unpublished internal economic analyses either from state MLIP administrators. Ultimately, the current evidence for the effects of MLIPs exists almost entirely to demonstrate the financial viability of operating MLIPs and makes very little attempt to shed light on the ability of MLIPs to influence public health outcomes related to nonmedical controlled substance use.

Literature gap 1: There exists a lack of rigorous, peer-reviewed evidence for the effectiveness of MLIPs in preventing risky controlled substance use and diversion in Medicaid populations. Understanding the role of MLIPs in combating the epidemic of nonmedical controlled substance abuse will require researchers to conduct high quality examinations of MLIP effectiveness. Addressing the

dearth of MLIP literature available to researchers, policymakers, and MLIP administrators provides significant motivation for investigating all aims of this dissertation. Further, no one has conducted a peer-reviewed examination of the North Carolina Medicaid Recipient Management Lock-In Program, specifically. While a peer-reviewed MLIP investigation from any state would provide broad lessons for the general landscape of controlled substance lock-in programs, the high variability across state MLIPs in program design means that one state's MLIP evaluation may have limited generalizability to other state MLIPs. The findings of this dissertation will provide the first peer-reviewed, highly actionable evidence for MLIP administrators in North Carolina, who represent the most immediate audience of this dissertation research.

The available body of published and unpublished evidence overwhelmingly indicates that MLIPs have positive impacts on reducing Medicaid service utilization measures—prescription, controlled substance, emergency care, and inpatient care—as well as use of multiple prescribers and multiple pharmacies. MLIPs also provide states with significant economic savings stemming from reduced use of pharmacy and medical services.

Literature gap 2: Aside from Kachur's investigation of all-cause mortality as a secondary outcome[112], no peer-reviewed study has examined the link between MLIP enrollment and major clinical outcomes, such as overdose events or overdose-related mortality. The aims of the present dissertation project do not directly investigate the association between MLIP enrollment and major clinical outcomes. However, the parent project from which this dissertation was formed addresses this gap, allowing this dissertation to fill additional gaps pertaining to known, but previously unexamined, limitations of the MLIP policy approach.

A major limitation of the MLIP policy strategy is the possibility of enrollees circumventing lock-in restrictions by purchasing controlled substance prescriptions completely out of pocket. This circumvention behavior wastes program resources and mitigates any intended effect of MLIP enrollment on regulating access to controlled substances for patients that abuse or divert these drugs. Circumvention also obviates the intended enhancements in care coordination for these high-risk patients. One

unpublished source provided initial estimates of a high prevalence of circumvention behavior in their MLIP population.[118] Additionally, reported findings of reduced controlled substance utilization trends following MLIP enrollment—particularly those by Keast[119]—could feasibly reflect an artifact of MLIP enrollment inducing circumvention, which cannot be captured solely in Medicaid claims data.

Literature gap 3: There has been no effort in the peer-reviewed literature to understand the prevalence or predictors of circumvention behavior among MLIP enrollees. Prior MLIP-related research has identified the MLIP circumvention limitation as a priority for future investigation of the feasibility of this policy intervention in achieving a public health benefit in the fight against prescription drug abuse.[106,112] Aim 1 of this dissertation directly addresses this gap by examining the prevalence and predictors of engaging in MLIP circumvention in North Carolina. More specifically, Aim 1 describes trends in circumvented opioid and benzodiazepine prescription fills in the NC MLIP program and attempts to isolate the effect of NC MLIP enrollment on the likelihood and extent of controlled substance circumvention.

Assessing the total threat of circumvention to the effectiveness of MLIPs in reducing prescription drug abuse behaviors and outcomes also requires an understanding of MLIP enrollees' controlled substance use risk profile occurring through circumvention.

Literature gap 4: Building on the previously identified literature gap, there has been no effort in the peer-reviewed literature to describe controlled substance prescriptions obtained by MLIP enrollees through circumvention. There has also been no effort to investigate the potential effect of MLIP enrollment on prescription-level measures of high-risk controlled substance use through circumvention, which knowingly occurs outside Medicaid's scope of influence. Aim 2 fills this gap in knowledge by describing trends in receipt of Schedule II opioids, long-acting opioids, and high-dose opioid prescriptions across payment sources before and after MLIP enrollment. Aim 2 also attempts to isolate the effect of NC MLIP enrollment on receipt of Schedule II and long-acting opioid prescriptions and on the average prescribed daily opioid dose. This information provides new evidence for any unintentional effect of MLIP enrollment on the degree of opioid use risk occurring through circumvention. Aim 2 also

elucidates whether certain opioid prescription characteristics have higher appeal for circumvention, which may inform targeted program optimizations to improve adherence to MLIP restrictions.

Additionally, to our knowledge, no one has utilized a dataset linking Medicaid claims data with the state's PDMP data in any peer-reviewed investigation of Medicaid beneficiaries' controlled substance utilization. The novel dataset linking Medicaid claims and PDMP data in Aim 1 to the peer-reviewed MLIP evidence base as a tool for monitoring MLIP enrollees' utilization patterns.

2.3 LITERATURE REVIEW—DEFINING HIGH-RISK OPIOID USE

2.3.1 Section Overview

Enrollment criteria for state Medicaid lock-in programs are largely comprised of thresholds for the number of controlled substance prescription fills, number of prescribers writing controlled substances, and/or number of pharmacies dispensing controlled substances in a pre-defined time period. As indicated in Table 2.3 from Section 2.1.11, however, the specific criteria utilized by MLIP administrators vary widely from state to state.[15] This lack of consistency in MLIP enrollment criteria suggests either a lack of evidence from which state MLIP administrators can base these decisions or a lack of consensus as to how best to apply the evidence.

In order to assess the evidence-base available to inform the design of MLIP enrollment criteria that are most likely to identify beneficiaries at the greatest risk of controlled substance-related adverse outcomes, this section presents relevant findings from a rigorous review of the peer-reviewed literature examining claims-based definitions for high-risk controlled substance utilization behaviors. A summary is provided at the end of Section 2.3, which also identifies gaps in the literature. Findings from this review of the literature provided a foundation for Aim 3 analyses. In this aim, we examined claims-based definitions of high-risk opioid analgesic use in North Carolina Medicaid that were most predictive of overdose-related events, signifying patients most likely to benefit from MLIP enrollment. To conduct this literature review we used PubMed, Google Scholar, Web of Science, and PsycINFO databases. We conducted free-text, as well as Boolean search strategies, to extract relevant studies published prior to May 2015 using key search terms such as, "controlled substance," "opioid," "benzodiazepine,"

"overdose," "death," "shopping," "doctor shopping," "pharmacy shopping," "high risk," "abuse," "misuse," and "nonmedical." We performed secondary reviews of article bibliographies to obtain additional relevant pieces of evidence not identified in the initial literature search.

2.3.2 Defining Risky Controlled Substance Use—Peer-Reviewed Literature

We first present findings from one study that explicitly investigated claims-based definitions of high-risk controlled substance use in the context of a Medicaid controlled substance lock-in program. We then organize the rest of the findings from our review of the published literature pertaining to claims-based strategies for defining high-risk opioid use by type of measure utilized in Aim 3 analyses: opioid prescription count, opioid prescriber count, opioid pharmacy count, daily opioid dose, and daily acetaminophen dose. We also include an "Other measures" subsection that describes alternative approaches to defining high-risk opioid use that are not explicitly investigated in the proposed dissertation. However, touching on these high-risk opioid definitions not employed in Aim 3 analyses provides a comprehensive review of all prior work done in this field that can inform future MLIP eligibility criteria validation research.

2.3.2.1 Wisconsin Medicaid Lock-In Program Eligibility Tool Study

Wisconsin Medicaid developed and tested a new automated decision tool for identifying beneficiaries for lock-in enrollment that would replace their manual review process.[150] The authors used chi-squared automatic interaction detection analyses to determine which combinations of controlled substance utilization measures were most predictive of risky controlled substance use. Qualifying medication classes included opioids, benzodiazepines, sedative hypnotics, stimulants, skeletal muscle relaxants, and barbiturates. Their eight utilization measures included overlapping prescription days supply of same-class drugs (2 and 6-month measures), number of same-drug prescription refills overlapping by 50% (2 and 6-month measures), number of same-day duplicate prescriptions using different providers, total number of controlled substance claims, number of total prescribers used, and number of total pharmacists used. The predictive ability of the decision tool was tested with 190 Wisconsin Medicaid beneficiaries that had been tapped for lock-in enrollment, receipt of a warning letter, or no further review

by through manual claims review performed by clinicians. The model correctly assigned lock-in enrollment 95% of the time, with a sensitivity and specificity of 87% and 96%, respectively. Table 2.4 presents the controlled substance utilization criteria that the decision support tool analyses identified as having statistically significant success in identifying beneficiaries that expert manual review tapped for lock-in enrollment, presented roughly in order of increasing rigor. Ultimately, the number of pharmacies used in six months was most predictive, followed by the number of overlapping days of controlled substance supply.

Table 2.4: Controlled Substance Overuse Criteria Identified as Significant by the Wisconsin Medicaid Decision Support Tool

[4 to 7 pharmacies]
[4 to 7 pharmacies] + [1-188 overlap days in 2 months]
[4 to 7 pharmacies] + [1-188 overlap days in 2 months] + [≥8 prescribers]
[4 to 7 pharmacies] + [≥189 overlap days in 2 months]
[4 to 7 pharmacies] + [≥189 overlap days in 2 months] + [≥314 overlap days in 6 months]
[≥8 pharmacies]
[≥8 pharmacies] + [128-313 overlap days in 6 months]
[≥8 pharmacies] + [≥314 overlap days in 6 months]

Note: Measures assessed over a 6-month period. Measures denoted as 2-month measures were assessed over the most recent 60 days.
Source: Mailloux AT, Cummings SW, Mugdh M. A decision support tool for identifying abuse of controlled substances by ForwardHealth Medicaid members. *Journal of hosp marketing & public relations.* 2010;20(1):34-55.

2.3.2.2 Claims-Based High-Risk Opioid Use Measures—Opioid Prescription Counts

Table 2.5 summarizes key claims-based definitions of high-risk opioid use from relevant peer-reviewed literature that were either developed through study analyses or defined by the researchers a priori. The table is organized by year published and lists the lead author, study population, the study outcome predicted by the measure (or if the measure was defined a priori), the observation period in which the opioid utilization measure was assessed, and threshold levels for the five key measures of high-risk opioid use utilized in Aim 3 analyses—opioid prescription count, prescriber count, pharmacy count, daily dose, and daily acetaminophen dose.

Table 2.5: Summary of Key Claims-Based Measures of High-Risk Opioid Use in Peer-Reviewed Literature

Study	Patient population	Outcome predicted	Obs. period (mo.)	Rx count	Prescriber count	Pharm. count	Opioid dose (MME/day)	APAP dose (mg/day)
Parente, et al (2004)	Privately insured	Expert chart review	Any		≥6	≥4		4000mg
Buurma, et al (2008)	Netherlands	"Drug-seeking" behavior	12			≥5		
Hall, et al (2008)	West Virginia residents	Overdose death	12		≥5 (CS)			
Braker, et al (2009)	Medicaid (MI)	N/A (researcher-defined)	6	≥3	≥2			
White, et al (2009)	Privately insured (ME)	Opioid abuse Dx	3	≥4	≥2	≥2		
			12	≥12		≥3		
Braden, et al (2010)	Medicaid (AR), private	Drug-related event	6				≥120mg	
Dunn, et al (2010)	HMO	Overdose event	3				≥50-100mg	
Katz, et al (2010)	Massachusetts residents	"Drug-seeking" behavior	12		≥4 (CII)	≥4 (CII)		
Sullivan, et al (2010)	Medicaid (AR)	Novel risk score	6				≥120mg	
Bohnert, et al (2011)	US Veterans	Overdose death	Varied				≥50mg	
Gomes, et al (2011)	Ontario, Canada residents	Overdose death	4				≥200mg	
Wilsey, et al (2011)	California residents	"Drug-seeking" behavior	12		≥5			
Cepeda, et al (2012, 13)	Population-based	"Drug-seeking" behavior	18					
Paulozzi, et al (2012)	New Mexico residents	Overdose death	6	≥6 (CS)			≥120mg	
Peirce, et al (2012)	West Virginia residents	Overdose death	6		≥4 (CS)	≥4 (CS)		
Rice, et al (2012)	Privately insured	Opioid abuse Dx	12	≥6		≥3		
Liu, et al (2013)	Privately insured	N/A (researcher-defined)	12				≥100mg	
McDonald, et al (2013)	Population-based	"Drug-seeking" behavior	12		≥10			
Weiner, et al (2013)	Population-based	N/A (researcher-defined)	12	≥4	≥4			
Baumblatt, et al (2014)	Tennessee residents	Overdose death	12		≥4	≥4	≥100mg	
Han, et al (2014)	California residents	N/A (researcher-defined)	12		≥5 (CII)			
Huffman, et al (2015)	Substance use clinic	Opioid addiction Dx	Varied				≥76mg	
Yang, et al (2015)	Medicaid	Overdose event	3			≥4		

Note: All findings reported in the table refer to opioid utilization unless otherwise specified. Rx=prescription; Pharm=Pharmacy; MME=Milligram morphine equivalent; mg=milligram; APAP=acetaminophen; CS=controlled substances; MI=Michigan; N/A=not applicable; ME=Maine; Dx=diagnosis; AR=Arkansas; HMO=health maintenance organization; CII=Schedule II; US=United States.

Five peer-reviewed articles offer an explicit threshold for the number of opioid prescriptions received by a patient indicating potential high-risk use behaviors. In a 2009 article in the *American Journal of Managed Care*, White, et. al., investigated predictors of opioid abuse diagnoses among 116,382 privately insured Maine residents using opioids between the ages of 12 and 64.[151] The authors used a stepwise multivariable logistic regression approach to evaluate the strength of association between various potential predictors and the presence of an opioid abuse diagnosis in claims data, controlling for age, sex, mental health diagnoses, and overall healthcare utilization. Their model containing measures for number of opioid prescriptions, number of pharmacies, number of early opioid fills, and opioid dose escalation variables was highly predictive of opioid abuse outcomes, with a Receiver Operating Characteristic c-statistic of 0.84. In terms of prescription quantity, White reports that having four or more opioid prescriptions in a three-month time period or 12 or more prescriptions in a 12-month time period were significantly associated with an opioid abuse diagnosis.

Paulozzi, et. al., conducted a retrospective case control study using a sample of 300 New Mexican residents over the age of 10 that died of drug overdose between 2006 and 2008, with 5,993 matched controls.[144] Paulozzi found that filling six or more controlled substance prescriptions of any class during a six-month exposure period quadrupled the mortality risk.

Rice, et. al., published a study in 2012 investigating prescription utilization behaviors associated with diagnosed opioid abuse in a large, nation-wide administrative claims database of privately insured individuals with prior opioid use.[152] In descriptive analyses, study subjects with diagnosed opioid abuse had an average of 13.3 opioid fills in the 12 months prior to the study index date, 2.4 pharmacies used, 3.2 prescribers used, and nearly 10% of opioid refills filled early. Using logistic regression analyses, Rice and colleagues found receipt of six or more opioid prescriptions in a 12-month period to increase the odds of opioid abuse seven-fold.

In addition, two articles utilized pre-determined prescription count thresholds to develop measures of high-risk opioid use patterns. In 2009, Braker used a cutoff of three or more opioid prescriptions during a six month observation period to screen for potential opioid misuse among

Michigan Medicaid beneficiaries.[153] In 2013, Weiner and colleagues defined high-risk opioid use as four or more opioid prescription fills in a 12-month span.[154]

2.3.2.3 Claims-Based High-Risk Opioid Use Measures—Opioid Prescriber Counts

Nearly a dozen studies describe high-risk opioid use in terms of the number of prescribers used. One of the earliest, and most rigorous, efforts to do so came in 2004 from Parente, et al, in 2004 when they sought to develop and validate explicit claims-based criteria for controlled substance misuse.[155] The authors created a multidisciplinary panel of experts who developed nearly 40 CS-PURE criteria, "controlled substance patterns of utilization requiring evaluation." Each criterion was operationalized using two large administrative claims databases comprised of a total of nearly four million privately insured lives under the age of 65. The authors then validated each criterion in 150 randomly-selected patient cases by modeling the association between the criterion and a controlled substance misuse score assigned by expert review. The best predictor of high-risk opioid use was the use of six or more prescribers of the same opioid product in any time period.

A few of these studies provide estimates of the association between number of opioid prescribers and adverse opioid-related clinical outcomes. The previously described 2009 study from White, et al, found that a threshold of two or more opioid prescribers in a three-month period was a strong predictor of opioid abuse diagnosis.[151] In a 2012 case control study among West Virginia opioid users, Peirce and colleagues found that use of four or more prescribers in a six-month time period was associated with double the odds of experiencing an opioid overdose-related death.[156] A similar case control design was recently employed in the population of all opioid users in the State of Tennessee by Baumblatt, et al. They found that receiving opioids from four or more prescribers in one year significantly increased the odds of opioid-related death by over 600%.[157]

The remaining literature offers a precedent of prescriber-based measures of high-risk opioid use by providing examples of researcher-defined thresholds for risky doctor shopping behaviors. Braker[153], Katz[158], and Weiner[154] all essentially used thresholds of 4 or more prescribers in a 12-month period to identify subjects with risky opioid use, while Hall[60], Wilsey[159], and Han[132] employed a cut-off of five or

more unique controlled substance prescribers in a 12-month period. In 2013, McDonald and colleagues identified 10 or more opioid prescribers in a year as an appropriate definition of risky doctor shopping in their analyses of a large, nationally representative sample of pharmacy fill data.[160]

2.3.2.4 Claims-Based High-Risk Opioid Use Measures—Opioid Pharmacy Counts

The majority of the articles describing opioid prescriber measures also investigated counts of pharmacies used by patients to obtain opioid prescriptions as a strategy for defining high-risk behaviors. The CS-PURE algorithm tool developed and validated by Parente and colleagues in 2004 found that use of four or more pharmacies to obtain the same opioid product within any time period was the second best indicator of high-risk use behind the number of prescriptions received.[155] Similarly, White found that two or more pharmacies in a three-month period, as well as three or more pharmacies in a 12-month period, was significantly associated with an increased probability of receiving an opioid abuse diagnosis.[151] Rice's previously described examination of the associations between opioid use patterns and the likelihood of being diagnosed with opioid abuse found that receiving opioids from three or more pharmacies in one year was significantly higher.[152] Peirce used a more stringent definition of pharmacy shopping in her case control study—four or more pharmacies in a six-month period—and found that pharmacy shopping was associated with a three-fold risk of opioid-related death.[156] The recent case control study from Baumblatt found a six-fold increase in the odds of opioid-related death in patients using four or more opioid pharmacies in one year.[157] The pharmacy threshold used by Baumblatt was partially based on Katz's prior success in defining pharmacy shopping as using four or more pharmacies for opioids in one year to identify high-risk patients.[158] Most recently, Yang and colleagues employed a threshold of four or more opioid dispensing pharmacies in a 90-day period as a claims-based predictor of opioid use disorder among a national population of Medicaid managed care patients.[161]

Additionally, Buurma, et. al., used the following definitions of pharmacy shopping to investigate predictors of this behavior: "light (all patients who visited more than one pharmacy at least once in 2001, except for patients defined as heavy or moderate shoppers), moderate (visited 3 or 4 pharmacies and had proportion of prescriptions elsewhere >10% and number of prescriptions elsewhere >10) or heavy (visited

5 or more pharmacies and had proportion of prescriptions elsewhere >10% and number of prescriptions elsewhere >10)."[162]

2.3.2.5 Claims-Based High-Risk Opioid Use Measures—Daily Opioid Dose

Multiple studies have used average daily opioid dose, measured in milligram morphine equivalents, to investigate the association between the amount of opioids received and adverse clinical outcomes like opioid overdose events and opioid-related deaths. In 2010, Braden and colleagues published one of the earliest studies attempting to identify a threshold level of MMEs associated with adverse opioid events. They conducted a retrospective cohort study in a database of private payer and Medicaid beneficiaries and ultimately found that an average opioid dose of 120mg/day over a six-month time period doubled the risk of a serious opioid event, when controlling for baseline demographic and clinical characteristics.[135]

Dunn and colleagues applied survival analysis methodologies to investigate the association between the average prescribed daily opioid dose and opioid overdose events in a sample of health maintenance organization beneficiaries with three or more opioid prescriptions in a 90-day period.[141] An average daily dose of 21-50mg of morphine equivalents was associated with a 50% increase in overdose risk, while doses of 51-100mg daily were associated with nearly four times the overdose risk of those with averages doses of 20mg or less. The authors found that once average daily opioid doses exceed 100mg morphine equivalents the risk for opioid overdose increased nine-fold.

Bohnert, et. al., conducted a case-cohort analysis in 2011 of 750 Veterans Health administration beneficiaries with unintentional opioid overdose-related deaths between 2004-2008, along with over 150,000 control subjects with opioid use during the observation period.[140] After adjusting for various clinical and demographic measures, they found daily doses of 50mg morphine equivalents or more to mark a significant increase in the risk of opioid-related mortality for patients with both chronic and acute indications for opioid therapy.

Gomes and colleagues employed a similar methodology in a Canadian sample of 498 opioid overdose decedents, with 1,714 matched controls.[142] After substantial adjustment for various clinical and

demographic variables, an average daily dose of >200mg of morphine equivalents resulted in a substantial higher odds of death compared to those with <20mg of morphine equivalents per day (Odds ratio=2.88: 95% CI 1.79-4.63). All other intermediate daily dosing categories were insignificant predictors. The authors suggested a threshold of 200mg/day in morphine equivalents for significant risk for opioid-related adverse outcomes. Gomes substantiated this finding in a subpopulation of economically disadvantaged patients that same year.[163]

In 2012, Paulozzi's case control study of New Mexican opioid-related deaths found that having a daily average morphine equivalent dosage of 40mg or more increased the odds of opioid-related mortality by 1200%, and mortality risk increased as average daily MME increased until it plateaued at 200mg MED/day. In the discussion, the authors highlight a single opioid prescription equaling an average daily MED of 120mg/day or greater as a suggested cause for review. Additionally, this 120mg/day MME figure reflects a previously validated threshold[133,135] and Centers for Medicare and Medicaid services have recently directed Medicare Part D plan administrators to utilize this threshold of 120 MME/day as a claims-based screening tool for risky opioid abuse.[164]

More recently, though, Liu and colleagues defined high-risk opioid use with a threshold of 100mg/day MME[143], and Baumblatt demonstrated in his case control study of Tennessean opioid-related decedents that an average daily opioid dose of 100 MME/day was associated with 11 times the risk of opioid-risk death compared to controls.[157] Using logistic receiver operating characteristic modeling, Huffman, et al, identified 76.1 MME/day as the optimal threshold for predicting an opioid use disorder upon retrospective review of 199 patients of a pain rehabilitation program.[165]

2.3.2.6 Claims-Based High-Risk Opioid Use Measures—Daily Acetaminophen Dose

Only one study in the published literature—the 2004 analysis of the CS-PURE criteria from Parente, et al—considered using APAP dosage from opioid-APAP combination products as a strategy for identifying patients at high risk for opioid-related adverse events. Through the use of multidisciplinary expert input and validation through retrospective claims analysis, an average daily APAP dose of 4,000mg/day over any time period was one of the top-5 performing thresholds of high-risk opioid use.[155]

2.3.2.7 Claims-Based High-Risk Opioid Use Measures—Other Measures

Multiple alternative measures for defining high-risk opioid use in claims data were used in the peer-reviewed literature and are summarized in Table 2.6. These measures were not used in the proposed dissertation analyses, but they deserve mention here if only to guide potential future research regarding the development of standardized MLIP enrollment criteria. One study defined high-risk opioid use as receiving 210 days supply of opioids in one year.[166] Multiple studies considered aberrant opioid utilization patterns in the form of inappropriately early opioid refills and receipt of multiple overlapping opioid prescriptions.[131,143,151,152,161,167] White and colleagues measured notable opioid dose escalations over consecutive months as markers of inappropriate opioid utilization,[151] Bohnert, et al, assessed whether or not patients received only "as needed" opioid prescriptions compared to schedule opioid dosing[140], and Liu compared considered receipt of long-acting and extended release opioid preparations as a potential risk factor.[143] Interestingly, Rice was able to measure household opioid use and found that six or more household opioid prescriptions or an opioid abuse diagnosis in 12 months significantly increases a patient's likelihood of receiving an opioid abuse diagnosis.[152]

Table 2.6: Summary of Alternative Claims-Based Measures of High-Risk Opioid Use in Peer-Reviewed Literature

Study	Patient population	Outcome predicted	Observation period	Alternative high-risk opioid definition
Edlund, et al (2007)	US Veterans	Opioid abuse Dx	12 months	≥210 total days supplied
Buurma, et al (2008)	Netherlands	"Drug-seeking" behavior	12 months	>10% of all Rx filled elsewhere + >10 Rx filled elsewhere
White, et al (2009)	Privately insured (ME)	Opioid abuse Dx	6 months	≥1 early refill; ≥2 consecutive dose escalations
Sullivan, et al (2010)	Medicaid (AR)	Novel risk score	6 months	Novel opioid misuse scoring algorithm
Bohnert, et al (2011)	US Veterans	Overdose death	Variable	Receiving only Rx with "as needed" dosing schedule
Cepeda, et al (2012, 13)	Population-based	"Drug-seeking" behavior	18 months	≥2 overlapping Rx from 2 prescribers at ≥3 pharmacies
Peirce, et al (2012)	WV residents	Overdose death	6 months	Concomitant opioid/benzodiazepine use
Rice, et al (2012)	Privately insured	Opioid abuse Dx	12 months	Early refills; ≥6 household Rx fills; household opioid abuse Dx
Daubresse, et al (2013)	Privately insured	Novel risk score	3 months	Novel opioid misuse scoring algorithm
Liu, et al (2013)	Privately insured	N/A (researcher-defined)	12 months	Overlapping opioid Rx; Overlapping opioid/benzodiazepine Rx; LA/ER opioid use;
Yang, et al (2015)	Medicaid	Overdose event	90 days	Overlapping opioid Rx

Note: All findings reported in the table refer to opioid utilization unless otherwise specified. US=United States; Dx=diagnosis; Rx=prescription; ME=Maine; AR=Arkansas; WV=West Virginia; LA=long-acting; ER=extended release.

Additionally, two large-scale efforts have also been made in the literature to develop claims-based aggregate opioid risk scoring systems to identify high-risk patients. Researchers in 2010 built upon the work of Parente, et. al., to develop and validate an opioid misuse score in the context of the large-scale TROUP (Trends and Risks of Opioid Use for Pain) study.[133] The opioid misuse score was based on the assessment of days supply of short-acting opioids, days supply of long-acting opioids, number of pharmacies used, and number of prescribers used over a six-month period. Each of the four measures was scored on a scale of 0-2, and year-long opioid misuse scores were stratified into no misuse (0-1), possible misuse (2-4), and probable misuse (5-16). The authors validated the opioid misuse score in two insurance claims databases for years 2000-2005: one containing nearly 3.8 million privately insured beneficiaries and the other comprised of 128,000 Arkansas Medicaid beneficiaries.[133] Sullivan and colleague's opioid misuse score also had a strong, linear relationship with receipt of an opioid abuse diagnosis.

More recently, Daubresse and colleagues developed a different controlled substance misuse scoring algorithm for use in claims data.[168] The controlled substance use score was based primarily on the volume of controlled substance prescriptions filled, number of pharmacies and physicians visited, and rate of utilization of controlled substances (Table 2.7). The authors assessed utilization of all Schedule II through Schedule V drug classes over a 90-day observation period. Although the authors did not explicitly validate these criteria by investigating associations between scores and controlled substance-related overdose or mortality, they did express confidence in their controlled substance score's specificity while still identifying a sample of high utilizers of sufficient size for analysis and intervention.

Table 2.7: Controlled substance risk score component measures

Source of information	Weight
Volume of controlled substance claims	Assign half a point to the individual for each of their first 8 claims for a controlled substance; assign 1 point for each additional controlled substance claim thereafter
Number of unique pharmacies and prescribers	Based on the combined total of unique pharmacies and prescribers, assign 1 point for the first two unique entities; assign 1.5 points for each unique entity thereafter
Rate of utilization of controlled substances	Assign 1 point if the number of claims for controlled substances in the 3rd month of the 90-day pre-intervention is two or more than the number of claims in the 2nd month of the pre-intervention period

Source: Daubresse M, Gleason PP, Peng Y, Shah ND, Ritter ST, Alexander GC. Impact of a drug utilization review program on high-risk use of prescription controlled substances. *Pharmacoepidemiol Drug Saf.* Jul 24 2013.

2.3.3 Defining Risky Controlled Substance Use—The "ADOPT" Report

In addition to the published literature, a 2012 CDC grant report detailed results from a recent initiative to develop a tool that predicts the effectiveness of Medicaid lock-in programs based on a state's MLIP enrollment criteria and characteristics of their Medicaid population.[169] The end result of this project was the "Approaches to Drug Overdose Prevention Analytic Tool" (ADOPT), an Excel-based simulation tool that produces predictions of clinical, utilization, and economic outcomes based on an MLIP's design and beneficiary population. Although ADOPT is yet to be validated in the peer-reviewed literature, the authors conducted extensive analyses into the associations between overdose-related events and controlled substance dosing and utilization patterns, which informed the development of the ADOPT simulation method. Findings from these analyses, like the literature discussed previously, have direct implications for the development of actionable definitions of high-risk opioid use.

Melnikow, et. al., used a large, nationally-representative administrative claims database to create a cohort of nearly 430,000 Medicaid managed care beneficiaries ages 12 and older with any opioid use in years 2008-10 and 24 months of continuous enrollment. A total of 1,738 opioid overdose events were identified in the sample. In primary analyses, average opioid doses of 50-100mg/day and >100mg/day, measured in morphine equivalents over 90 day periods, were associated with a significant three-fold and five-fold increase in overdose risk compared to average doses of <20mg/day.

Secondary analyses looked at measures of overlapping prescriptions and pharmacy shopping. Overlapping prescriptions was defined as obtaining an opioid prescription fill with at least 25% of a previous opioid fill remaining. Comparative measures of pharmacy shopping were evaluated based on capture of overdose events among variations on use of three or four pharmacies assessed over observation periods of 90, 180, and 365 days (Table 2.8). The authors selected a threshold of four or more pharmacies in a 90-day period as an operational definition of pharmacy shopping. In descriptive analyses looking at varied combinations of the pharmacy shopping and overlapping prescription criteria, a definition of risky opioid-seeking behavior combining pharmacy shopping and overlap was most effective at identifying those ultimately experiencing overdose events, followed by an overlapping prescription-only definition.

Table 2.8. Comparison of Different Pharmacy Shopping Criteria in Medicaid MarketScan® Dataset

Pharmacy shopping criteria	Eligible recipients	Overdose events	% Overdose among eligible recipients	% of total overdose	DOR
1-year setting, ≥3 pharmacies	44,266	825	1.86%	69.86%	2.38
1-year setting, ≥4 pharmacies	29,175	620	2.13%	52.50%	2.3
180-day setting, ≥3 pharmacies	38,157	818	2.14%	69.26%	3.05
180-day setting, ≥4 pharmacies	21,351	599	2.81%	50.72%	2.73
90-day setting, ≥3 pharmacies	28,730	788	2.74%	66.72%	4.28
90-day setting, ≥3 pharmacies	13,083	555	4.24%	46.99%	5.23

DOR= Diagnostic odds ratio
Reproduced from: Melnikow J, Yang Z, Soulsby M, Ritley D, Kizer K. *Approaches to Drug Overdose Prevention Analytical Tool (ADOPT): Evaluating Cost and Health Impacts of a Medicaid Patient Review & Restriction Program.* University of California, Davis; December 2012.

The measures of pharmacy shopping and overlapping opioid prescriptions were then included in the previous analytic model predicting overdose risk based on opioid dosing strata. Dosing categories of 50-100mg morphine equivalents per day and >100mg/day remained highly predictive of opioid overdose events. Pharmacy shopping and overlapping opioid prescriptions significantly increased the risk of overdose 80% and 200%, respectively. The authors recommend using thresholds of 100mg mean morphine equivalents per day, the presence of 25% overlap in similar opioid prescriptions, and use of four or more pharmacies in a 90-day period as criteria for identifying Medicaid beneficiaries at greatest risk of adverse opioid-related outcomes.

2.3.4 Defining Risky Controlled Substance Use—Summary and Gaps

There is general consistency in the literature regarding measures of high-risk opioid use. The evidence overwhelmingly supports the use of number of pharmacies visited, number of prescribers used, number of controlled substance prescription fills, and average daily dose of opioid analgesics, measured in morphine equivalents. Additional measurement strategies have been used with some success: presence of overlapping controlled substance prescriptions[131,150,152,155,167,169], accelerated opioid use[151,168], total opioid days supplied[166], daily APAP consumption (from opioid analgesic combination products)[155], and

household opioid utilization patterns[152]. There is less consistency in the actual measurement thresholds used to delineate risky use, as well as observation periods over which these measures should be assessed. The most agreement seems to be found in recommendations to use high-risk thresholds of 2-5 pharmacies, 2-5 prescribers, and average daily morphine equivalent doses of opioids of 50-120mg/day, assessed over 6 to 12-month periods.

Literature gaps: There is scant evidence in the peer-reviewed literature, to date, explicitly investigating the development of definitions of high-risk opioid use for the purpose of creating effective and standardized Medicaid lock-in program eligibility criteria.[150] One peer-reviewed article detailed the development of an automated claims-based algorithm for the purpose of identifying MLIP-eligible beneficiaries.[150] However, the authors only evaluated the ability of their algorithm to predict agreement with previous MLIP enrollment decisions based on retrospective manual case review and not actual adverse clinical outcomes that MLIPs are intended to prevent. Additionally, the results of this study have limited generalizability to state MLIPs outside of Wisconsin, including the NC MLIP. The ADOPT Report from Melnikow, et. al., also rigorously evaluated the association between opioid utilization behaviors and opioid overdose events in Medicaid beneficiaries for the purpose of informing MLIP design.[169] However, its study sample did not included Medicaid fee-for-service beneficiaries, and it used a multi-state pooled sample of Medicaid patients (most of which likely lived in states with active MLIPs that may have biased results). Also, ADOPT analyses were conducted to inform the development of an MLIP outcomes simulation tool estimating the effects of an MLIP based on pre-determined eligibility criteria and not to inform the development of optimal MLIP enrollment criteria strategies for individual states. These gaps in knowledge motivated Aim 3 of this dissertation in which we sought to identify and validate measures of high-risk opioid use that are most predictive of downstream adverse clinical outcomes from opioid abuse. These findings would inform standardized MLIP eligibility criteria.

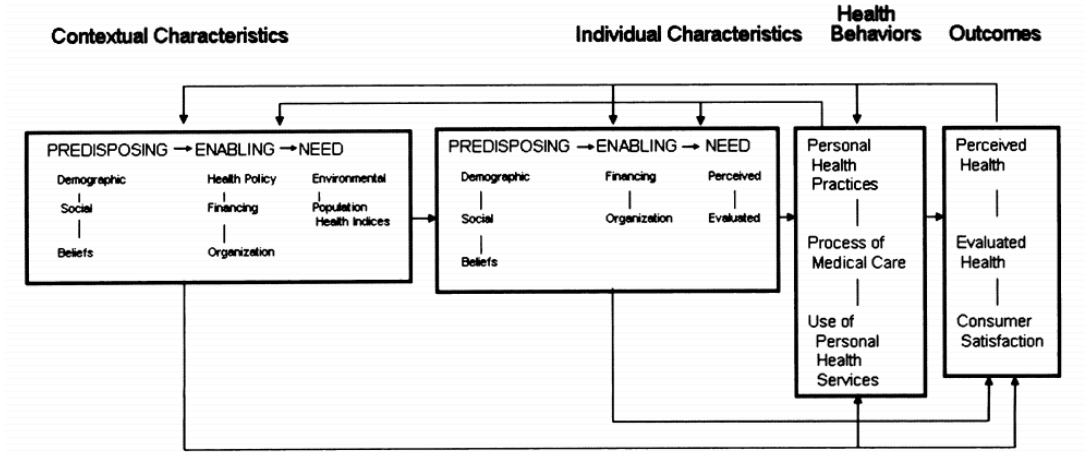
2.4 CONCEPTUAL MODEL

This dissertation research was designed based on Andersen's Behavioral Model of Health Service Use, a theoretical framework illustrating the associations of individual and contextual factors with health behaviors and outcomes.[170] In general, the Andersen model states that a patient's health service utilization is a product of non-modifiable characteristics predisposing a patient to certain health behaviors and outcomes; enabling characteristics that facilitate or hinder healthcare use; and their need for health services.[171]

2.4.1 Andersen's Behavioral Model of Health Services Use

The Andersen Behavioral Model of Health Service Use was first introduced in the 1960s for the purpose of guiding the research and development of health policies to ensure equitable access to healthcare across patient populations.[170] The model was intended to achieve these ends by helping establish standardized definitions and measures of myriad factors thought to influence access to care. Since its introduction in the literature, the Andersen model has been expanded and revised numerous times, with the fifth—and most recent—revision occurring in 2008. Figure 2.2 portrays the fifth phase of the Andersen model. The most notable change to the Andersen model seen in Phase 5 is the recognition that contextual determinants of healthcare use on the aggregate healthcare system-, community-, and provider-levels can also be conceptualized as predisposing, enabling, and need characteristics.

Figure 2.1: Andersen's Behavioral Model of Health Services Use (Phase 5, 2008)



Reproduced from: Andersen RM. National health surveys and the behavioral model of health services use. *Med Care.* Jul 2008;46(7):647-653.

Individual characteristics that predispose patients to use healthcare services include patient demographics (such as age and gender), social characteristics (such as race and education level), and personal beliefs and values concerning health and healthcare.[170] Enabling characteristics of the individual, such as income and health insurance coverage, work to regulate accessibility of healthcare services. Lastly, individual need characteristics represent the evaluated clinical need for services as well as perceived need. All types of individual characteristics are influenced by contextual determinants of healthcare use. These include the predisposing factors like the age and social structure of the community; enabling factors like the supply of accessible healthcare facilities and providers in the area; and the community need for healthcare services based on the health status and comorbidities of the population.

Individual and contextual characteristics determine patient and provider health behaviors, including personal health practices, processes of medical care, and use of personal health services.[170] Personal health practices encapsulate individual behaviors that alter or maintain health such as dieting, exercising, and smoking. Processes of medical care represent provider behaviors with regard to diagnostic and therapeutic activities undertaken in the course of patient care. Use of health services refers to

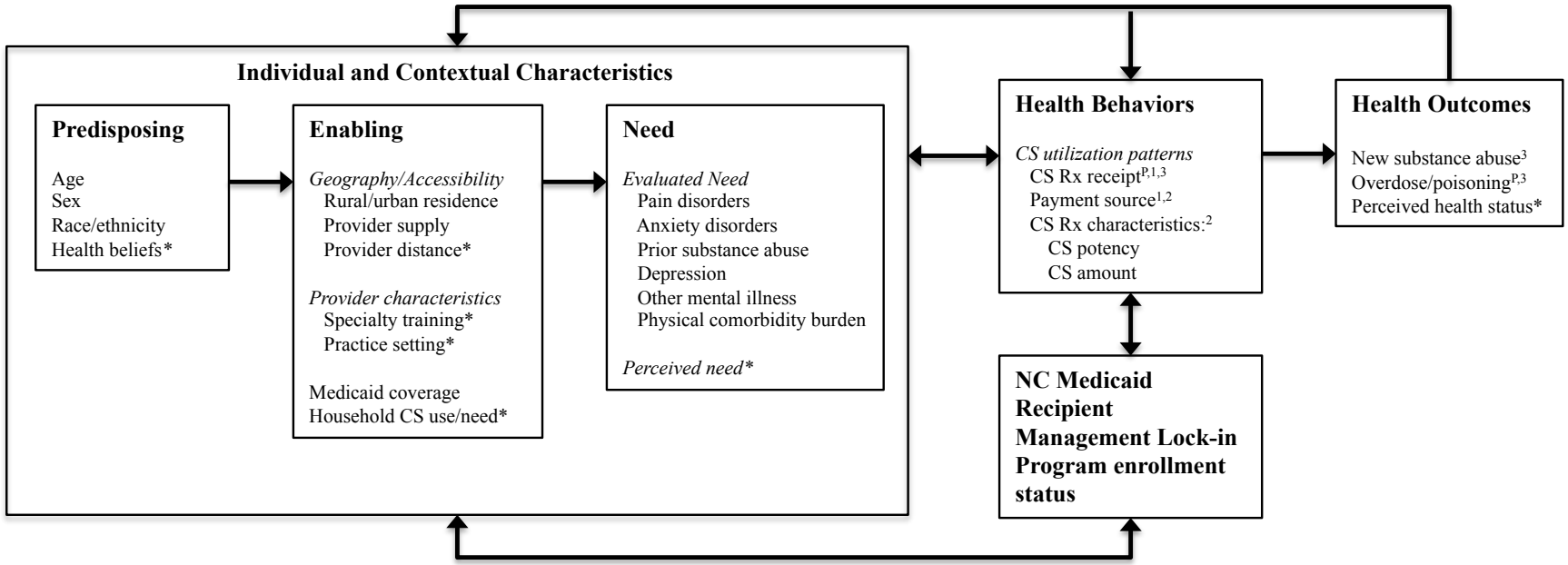
patients' use of the healthcare system, such as through pharmacy, outpatient, inpatient, and emergency care visits.

Health outcomes in the Andersen model include evaluated clinical benefits and harms from healthcare; patients' perceived health; and patient satisfaction with care.[170] Health outcomes are influenced by contextual characteristics, individual characteristics, and health behaviors. Health outcomes are also capable of impacting these factors in the pursuit of future healthcare services.

2.4.2 Dissertation Conceptual Model

Figure 2.3 depicts the conceptual model informing the investigation of the dissertation aims, as well as the outcomes of the parent project. The conceptual model is a modified version of the Andersen Behavioral Model of Health Services Use. The individual and contextual characteristics were consolidated for ease of interpreting predisposing, enabling, and need characteristics. The NC MLIP policy intervention was also introduced to the conceptual model as a unique determinant of health behaviors in the NC Medicaid population.

Figure 2.2: Dissertation conceptual model based on Andersen's Behavioral Model of Health Service Use



Note: *unobservable; CS=Controlled substance; Rx=Prescription; NC=North Carolina
P=Parent project outcome of interest; 1=Aim 1 outcome of interest; 2=Aim 2 outcome of interest;
3=Aim 3 outcome of interest (overdose event health outcomes used for the purpose of validating high-risk CS utilization health behavior measures)

2.4.2.1 Dissertation Conceptual Model—Predisposing Characteristics

Measurable predisposing characteristics in the conceptual model include age, sex, and race/ethnicity. Nonmedical use of controlled substances and its related consequences have been shown to be associated with each of these variables. The evidence overwhelmingly indicates that young and middle-aged adults, roughly ages 20-50, receive controlled substance prescriptions most frequently[39,42,132,137,172,173] and are most likely to nonmedically use prescriptions[1,52,53,133,174,175], engage in doctor/pharmacy shopping[60,132,162], receive opioid abuse diagnoses[54,137,166,176,177], and experience overdose events and overdose-related death.[2-4,59,60,173] The age range of 45-54 years exhibits the greatest risk for opioid-related deaths in the US, according to the CDC.[3]

Conflicting evidence exists over the prevalence of controlled substance utilization between the sexes.[39,42,178,179] However, the literature does indicate that male sex is associated with greater dose escalation of opioid analgesics[172] and increased nonmedical use behaviors.[1,52,175,179] In 2012, lifetime prevalence of nonmedical controlled substance use was 15.9% for men and 11.2% for women in the US.[180] Non-medically used controlled substances were more likely to be received from a friend or family member for men[180], while women were more likely to engage in doctor- and pharmacy-shopping behaviors.[60,162] Male nonmedical users of controlled substances are at a much greater risk of receiving an opioid abuse diagnosis[54,166,181] and experiencing overdose-related death compared to women. [2,3,60,173]

Additionally, non-Hispanic White and Native American individuals report the most nonmedical use of prescription drugs[52,182] and also have the greatest controlled substance-related mortality risk of all races and ethnicities.[2,4,173] Patient health beliefs also serve as a key predisposing characteristic, but this factor was not measurable in the study data.

2.4.2.2 Dissertation Conceptual Model—Enabling Characteristics

Enabling variables in the conceptual model include measurable characteristics thought to facilitate the accessibility of health services of interest in the dissertation. These primarily included county-level measures that capture rural residence. Rural residence has been theorized as a key driver in substance abuse[183] and has previously been associated with an increased risk of nonmedical use[51],

diagnosed opioid abuse[73,184], and controlled substance overdose events.[2,56] Multiple studies have shown that opioid abuse and overdose is heavily concentrated in the Appalachia region of the United States, which includes western parts of North Carolina.[184,185] Increased local supply of physicians and pharmacies—a marker of metropolitan residence and increased accessibility of healthcare services—also results in higher levels of prescriber- and pharmacy-shopping.[186]

Additionally, provider-level characteristics of specialty training, location, and practice setting serve as enabling factors in the conceptual model. Previous research shows that prescriber specialty training is predictive of increased opioid prescribing compared to primary care providers.[187] Inappropriate controlled substance shopping behaviors are associated with traveling increasing distances from a patient's home to the controlled substance prescriber.[188] The prescriber's practice setting, namely the emergency department setting, is associated with increased likelihood of opioid prescribing.[187] Pharmacy characteristics, such as chain vs. independent, may help predict controlled substance use patterns. However, the data sources used in this dissertation did not allow for reliable assessment of provider- and pharmacy-level characteristics, but this highlights a rich area for future MLIP research.

Although the study population consists entirely of North Carolina Medicaid beneficiaries, Medicaid coverage status was included in the conceptual model to recognize its role in enabling healthcare service use. Also, the conceptual model recognizes household controlled substance utilization and opioid abuse diagnoses as key predictors of nonmedical use[181], despite the fact that this was not measurable in the study data.

2.4.2.3 Dissertation Conceptual Model—Need Characteristics

The primary evaluated need characteristics in the conceptual model pertain to diagnosed conditions for which opioid analgesics and benzodiazepines are indicated. These include chronic non-cancer pain diagnoses[189] and anxiety disorder diagnoses, respectively. Additionally, an increased burden of comorbid conditions—primarily mental health and co-occurring substance abuse conditions—are known predictors of nonmedical prescription use and its subsequent outcomes.[190] Mental illness, such as depression, anxiety disorders, and mood disorders, are all associated with increased utilization of

controlled substances[191-195], nonmedical use behaviors[196-199], and diagnosed opioid abuse.[67,166,176,181,200] Researchers estimate having one of these conditions results in a 2-3 times higher risk of nonmedical use and opioid abuse, compared to those without mental health conditions.[181,198] Similarly, a history of co-occurring substance abuse, including alcohol and illicit street drugs, also was associated with higher controlled substance utilization[192-194], nonmedical use[7,51,175,182,196,199], and opioid abuse[66,67,166,176,181], in addition to opioid overdose-related death.[140]

Other physical comorbid burden, such as chronic diseases like hypertension, are also included in the conceptual model as need characteristics. The overall health status and comorbidity burden have been shown to be worse among patients receiving controlled substance medications.[201-204] Physical comorbidity burden also helps to explain the extent to which patients interact with the healthcare system. Perceived need was recognized in the model as an important factor in patients' healthcare seeking behaviors; however, perceived need was not measurable in the dissertation data.

2.4.2.4 Dissertation Conceptual Model—NC Medicaid Lock-In Program Status

The main modification to the Andersen framework in the development of the dissertation conceptual model was the inclusion of an additional construct for NC MLIP enrollment status. As depicted, enrollment in the NC MLIP occurs as a function of individual and contextual predisposing, enabling, and need characteristics, as well as health behaviors around controlled substance use that contribute to eligibility for the program. Enrollment in the NC MLIP also modifies health behaviors by imposing provider access restrictions that are intended to influence patients' controlled substance utilization patterns. MLIP enrollment status would also have an effect on contextual and individual need characteristics. Accounting for the role of the lock-in program in the conceptual model as a stand-alone construct recognizes that other factors in the model impact eligibility and enrollment in the program and can also be subsequently influenced by MLIP enrollment. The effect of NC MLIP enrollment status on controlled substance-related health behaviors motivates the investigations of Aims 1 and 2.

2.4.2.5 Dissertation Conceptual Model—Health Behaviors

Predisposing, enabling, and need characteristics, as well as NC MLIP enrollment status, determined key patient health behaviors in this dissertation. The specific health behaviors of interest were controlled substance use behaviors that determine the effectiveness of MLIPs in mitigating high-risk controlled substance use. These controlled substance use behaviors included the receipt of controlled substance prescriptions, patient decisions regarding source of payment for controlled substance prescriptions (circumvention versus Medicaid coverage), and the types and characteristics of controlled substance prescriptions obtained by patients.

Aim 1 investigates the effect of NC MLIP enrollment on engaging in Medicaid circumvention to obtain controlled substances. Aim 1 was founded on a conceptual relationship in which NC MLIP enrollment is believed to induce people to circumvent Medicaid to obtain controlled substances. Unpublished sources suggest that circumvention is common in MLIP programs[118] and that further investigation of circumvention behavior is needed to improve the benefit of MLIPs through better lock-in adherence.[112] Circumvention is problematic, because it results in failure to achieve care coordination between designated lock-in providers, and it signals a failure to regulate access to controlled substances for those intent on abusing or diverting these medications.

Evidence of MLIP-induced circumvention reveals concerns over lock-in restrictions inadvertently causing some Medicaid beneficiaries to engage in high-risk controlled substance use behaviors knowingly occurring outside the purview of the Medicaid program.[112,118,130] High-risk controlled substance use, however, is not just a function of how frequently patients seek these medications. The characteristics of the controlled substance prescriptions themselves also contribute to high-risk use behaviors and outcomes. More specifically, high potency opioid agents and large dosages of opioids per prescription are associated with greatly increased risk of substance abuse disorders and overdose outcomes.[135,137,140,142,145,205] And unsurprisingly, high potency and high dosage opioid prescriptions are specifically sought by opioid abusers due to their enhanced euphoric effects and increased street value.[37,133,146,206-208] Therefore, Aim 2 examined the effect of NC MLIP enrollment on receipt of high

potency and high dosage opioid prescriptions through circumvention. This study was founded on the conceptual underpinning that NC MLIP restrictions may influence the use of these high-risk opioid products known to have greater appeal to opioid abusers, especially when purposely sought outside the purview of MLIP administrators.

In Aim 3, controlled substance utilization patterns comprised the independent variables predicting clinical outcomes from high-risk controlled substance use. Measures of controlled substance use in Aim 3 centered around the extent of controlled substance prescriptions received and providers used.

2.4.2.6 Dissertation Conceptual Model—Health Outcomes

Patient predisposing, enabling, and need variables; health behaviors; and NC MLIP enrollment status work in concert to determine key health outcomes in the conceptual model. These included the primary Aim 3 outcome of unintentional opioid analgesic overdose, as well as secondary Aim 3 clinical outcomes of unintentional APAP overdose due to opioid/APAP combination products, unintentional overdose of any drug product, diagnosed opioid use disorder, and diagnosed substance use disorder of any type. The secondary outcomes accounting for unintentional overdose and substance use disorder diagnoses from all drug products were assessed, because opioid analgesics readily contribute to these outcomes when in cocktail with other substances but may not be characterized in administrative claims data as the primary responsible agent.[4,20,60,61,209] Perceived health status is also an important health outcome; however, it was not evaluated due to the absence of self-reported health information in the study data.

2.5 CHAPTER SUMMARY

In Chapter II we provided background information detailing the recent epidemic of prescription drug abuse and misuse in the United States and major state-level policy strategies intended to prevent nonmedical use of controlled substances and its outcomes. We provided a comprehensive review of the peer-reviewed and grey literature for the effect of one specific and highly prevalent policy strategy, Medicaid controlled substance lock-in programs, on patient outcomes. Overall, we found a stark lack of rigorous evidence for the effect of MLIPs on patient outcomes and identified major gaps in the literature

motivating the research questions posed by the dissertation parent project and Aims 1 and 2 of this dissertation, which evaluate the North Carolina MLIP implemented in 2010. Specifically, the parent project addressed the lack of peer-reviewed literature around the effect of MLIPs on controlled substance Medicaid claims and the overdose outcomes. Aim 1 of this dissertation was designed to address the current lack of knowledge around the prevalence and predictors of lock-in circumvention, which is a notable limitation of the MLIP policy strategy. Aim 2 further addressed the limitation of MLIP circumvention by examining prescription-level characteristics of opioids obtained by MLIP enrollees through circumvention.

We also provided a rigorous review of the literature investigating claims-based definitions of high-risk opioid use to understand the evidence available to inform MLIP eligibility criteria, which varied significantly across states. Aim 3 of this dissertation was motivated by the lack of literature examining claims-based thresholds of high-risk opioid use in Medicaid claims data, specifically in the context of identifying beneficiaries most likely to benefit from MLIP enrollment with regard to overdose prevention.

We closed Chapter II by detailing a conceptual model based on the Andersen Behavioral Model of Health Service Use theoretical framework, which guided the investigations of each dissertation aim. This model conceptualized the relationship of subjects' predisposing, enabling, and need characteristics with their medication use behaviors; the North Carolina MLIP; and subsequent clinical outcomes.

CHAPTER III: METHODS

This chapter outlines the methodologies that were used to investigate the aims of this dissertation. More specifically, Chapter III describes the dissertation data sources, overall study design and population, measures used, and analytic approach for each aim, including cohort selection and statistical analysis. The aims of this dissertation were:

1) To examine the effect of the North Carolina Medicaid Recipient Management Lock-in Program, as well as patient-level characteristics, on controlled substance circumvention behaviors;
2) To investigate prescription-level characteristics of opioid analgesics obtained by North Carolina Medicaid Recipient Management Lock-In Program enrollees through circumvention.
3) To identify and validate the most effective measures of high-risk opioid analgesic use in the North Carolina Medicaid population.

3.1 DATA SOURCES

This dissertation used two primary quantitative data sources to conduct study analyses. The first data source, which was used in all aims of the dissertation, came from the North Carolina Division of Medical Assistance's (DMA) DRIVE database. DRIVE (Data Retrieval Information and Validation Engine) is a state-operated data warehouse that aggregates information about North Carolina Medicaid beneficiaries and their health service utilization.[210] More specifically, DRIVE provides detailed demographic information for Medicaid beneficiaries; detailed periods of Medicaid enrollment for individual beneficiaries; administrative claims data for prescription, outpatient, inpatient, and emergency care services paid by NC Medicaid; provider-level information; and administrative records of enrollment in the North Carolina Medicaid lock-in program. We used DRIVE data from 10/1/2008 to 9/30/2012, encompassing two years prior to and two years following NC MLIP implementation.

Data from North Carolina's CSRS comprised the second major quantitative data source and was used in Aims 1 and 2 analyses. The CSRS database is managed by the North Carolina Division of Mental Health, Developmental Disabilities, and Substance Abuse Services.[98] The CSRS provided records for each Schedule II, III, IV, and V medication dispensed by community and outpatient pharmacies in North Carolina. For each controlled substance prescription record, the CSRS data provided patient name, birthdate, address, and phone number; prescription written and filled dates; prescription number; indication of a new fill or refill; National Drug Code identifier of the prescribed medication, quantity dispensed, and days supply; pharmacy's DEA number; and prescriber's DEA number.[98] North Carolina pharmacies are required to report this information for each controlled substance prescription filled within 72 hours of its dispensation. Notably, the CSRS data do not contain information about payment source of controlled substance prescriptions. We used CSRS data from 10/1/2009 through 9/30/2012, which represented one year prior to and two years following NC MLIP implementation in October 2010.

The CSRS did not perfectly capture all Medicaid controlled substance prescription claims during the study period. A total of 6.6% of opioid and benzodiazepine Medicaid claims failed to produce a matching CSRS record among Medicaid prescription claims included in Aim 1 and 2 analyses. We examined these claims for evidence of systematic missingness that may have introduced bias into Aims 1 and 2 analyses (Appendix Table 1). There was no obvious evidence of meaningful systematic differences in Medicaid prescription claims that were captured vs. not captured by the CSRS with regard to relevant study measures. There was no statistically significant difference between these subsets of Medicaid claims with regard to subject gender and clinical comorbidity burden. There were statistically significant, but very small differences with regard to subject age, rurality of county of residence, and each of the three prescription-level outcomes investigated in Aim 2. The distribution of CSRS captured and non-captured Medicaid prescription claims were analogous across the duration of the study period, as well (Appendix Figure 1). Based on these findings, we assumed the 6.6% of missing Medicaid prescription claims in the CSRS dataset only contributed to conservative estimates of the prevalence and rate of circumvention behavior and did not introduce bias.

3.1.1 North Carolina Medicaid and CSRS Data Linkage

Aim 1 and 2 analyses utilized a dataset that links North Carolina Medicaid and CSRS data. An external individual hired by the parent project research team performed the CSRS and Medicaid data linkage. Because the CSRS and Medicaid datasets lacked a shared crosswalk, such as Medicaid ID or Social Security Number, patient-level name, date of birth, and address identifiers were used by the data programmer to manually perform systematic linkages for Medicaid beneficiaries that were enrolled at any point in the MLIP. All patient identifiers were removed prior to delivery of the final merged dataset to the researchers with encrypted Medicaid IDs used to identify individual subjects.

Distinct advantages and disadvantages exist with the merged North Carolina Medicaid and CSRS dataset. To our knowledge, this was the first instance of a peer-reviewed MLIP investigation linking these two data sources. This allowed the investigators to assess controlled substance-seeking behavior for MLIP enrollees that paid for these medications completely out-of-pocket, which Medicaid claims data is unable to detect. However, due to the lack of a shared crosswalk between the two datasets and the administrative burden of linking these data sources means that CSRS data were only available for NC MLIP enrollees. Therefore, the analytic dataset was unable to observe controlled substance cash payments among the full NC Medicaid population. This prevented any comparison between the subset of MLIP enrollees and the general Medicaid beneficiary population of the rates of Medicaid circumvention for obtaining controlled substances. Additionally, the CSRS dataset only captured controlled substance utilization behaviors within the State of North Carolina. Therefore, the linked Medicaid–CSRS dataset was unable to detect circumvention behaviors that occurred across state lines among NC MLIP enrollees.

3.2 OVERALL STUDY SAMPLE AND DESIGN

The dissertation evaluated the NC MLIP through a retrospective cohort design that included adults age 18-64 enrolled as a North Carolina Medicaid beneficiary at any point between 10/1/2008 and 9/30/2012. Adults eligible for Medicaid coverage in North Carolina included those with annual income less than 46% of the Federal Poverty Limit (FPL) who are working parents of dependent children, adults making less than 36% FPL who are non-working parents of dependent children, pregnant women making

less than 196% FPL, and disabled working and non-working adults.[211] Specific study population criteria differed by aim and are presented for each aim below in Section 3.5.

3.3 POWER CALCULATIONS

Statistical power of dissertation analyses was examined *a priori* in SAS 9.3. It was determined sufficient power existed for Aims 1-3 under reasonable, conservative assumptions from prior literature and current understanding of the study population and data sources. For Aims 1 and 2, approximately 4,500 individuals were enrolled in the NC MLIP during the first 18 months of the program, and based on prior literature of Medicaid enrollment it was expected 50% of these subjects would meet the continuous enrollment inclusion criteria.[212] For the dichotomous circumvention outcome we ignored the contribution of repeated measures to be conservative and assumed a 50% prevalence of circumvention.[118] We estimated having 80% power to detect a 19%, 16%, 13%, and 9% increase in odds of circumvention assuming possible within-subject correlations of 0.0, 0.25, 0.5, or 0.75, respectively. For the count outcome, we estimated over 90% power to detect a change in 0.5 circumvention events for the expected 1,125 circumventers, based on an assumed standard deviation of 5.0 and correlation of 0.5.

For Aim 3, we used the parent project's preliminary analyses of NC Medicaid claims data for the 12 months prior to the MLIP implementation to estimate that 300,000 adults filled an opioid prescription during our study period and 1,500 experienced an overdose event. We conservatively expected 50% of subjects to meet continuous enrollment inclusion criteria.[212] Therefore, after randomly dividing subjects into 50% subsamples, we anticipated an Aim 3 testing sample of 75,000 subjects with 375 overdose events. Assuming a null area under the curve (AUC) value of 0.70, this sample size would provide us with 95% power to determine whether the true AUC of our high-risk opioid measures in ROC analyses was 0.75 or greater at an alpha level of 0.05. And assuming that the true sensitivity of an opioid measure threshold was excellent at 90%, with 375 overdose cases in the validation sample we estimated having 80% power to conclude that the sensitivity was 85% or greater using a two-sided test and alpha of 0.05.

3.4 MEASURES

Measures used in dissertation analyses are defined in Table 3.1 and described below.

Table 3.1: Definitions and characteristics of dependent and independent variable measures used in dissertation analyses

Aim	Variable	Type	Time Variation	Data Source	Description
	Dependent Variables				
1	Circumvented fill	Dichotomous	Variant	Medicaid/CSRS	1=Present; 0=Absent
1	Circumvented fill	Count	Variant	Medicaid/CSRS	Number of circumvention events
2	Long-acting opioid fill	Dichotomous	N/A	Medicaid/CSRS	1=Long-acting opioid; 0=Short-acting opioid
2	Schedule II opioid fill	Dichotomous	N/A	Medicaid/CSRS	1=Schedule II opioid; 0=Schedule III-V opioid
2	Prescribed daily opioid dose	Continuous	N/A	Medicaid/CSRS	Average daily milligram morphine equivalents prescribed
3	Unintentional overdose, opioid	Dichotomous	N/A	Medicaid	1=Present; 0=Absent
3	Unintentional overdose, APAP	Dichotomous	N/A	Medicaid	1=Present; 0=Absent
3	Unintentional overdose, any drug	Dichotomous	N/A	Medicaid	1=Present; 0=Absent
3	Substance use disorder, opioid	Dichotomous	N/A	Medicaid	1=Present; 0=Absent
3	Substance use disorder, any drug	Dichotomous	N/A	Medicaid	1=Present; 0=Absent
	Independent Variables				
	Predisposing characteristics				
1,2	Age	Continuous	Variant	Medicaid	Patient age in years
1,2	Sex	Dichotomous	Invariant	Medicaid	1=Female; 0=Male
1,2	Race/ethnicity	Categorical	Invariant	Medicaid	White, Black, Other/unknown race
	Enabling characteristics				
1,2	Rural-Urban Continuum Code	Categorical	Variant	Medicaid/USDA	County rurality rating from 1=most metropolitan, 9=most rural
1,2	Metropolitan county	Dichotomous	Variant	Medicaid/USDA	1=RUCC of 1-3; 0=RUCC of 4-9
1,2	Prescriber supply count	Continuous	Variant	Medicaid/HPDS	Number of unique prescribers in a county
1,2	Pharmacy supply count	Continuous	Varian	Medicaid/NPPES	Number of unique community pharmacies in a county
1,2	Border county	Dichotomous	Variant	Medicaid	1=County of residence on NC border; 0=Not on border
	Need characteristics				
1,2	Any chronic non-cancer pain Dx	Dichotomous	Invariant	Medicaid	1=Present; 0=Absent
1,2	Any anxiety disorder Dx	Dichotomous	Invariant	Medicaid	1=Present; 0=Absent
1,2	Any substance abuse Dx	Dichotomous	Invariant	Medicaid	1=Present; 0=Absent
1,2	Any depression Dx	Dichotomous	Invariant	Medicaid	1=Present; 0=Absent
1,2	Any other MH Dx	Dichotomous	Invariant	Medicaid	1=Present; 0=Absent
1,2	Comorbid disease burden	Continuous	Invariant	Medicaid	Charlson Comorbidity Score, ranging from 0-37
1,2	Prescription drug burden	Continuous	Invariant	Medicaid	Number of unique drug therapy products received

Note: CSRS=Controlled Substances Reporting System; APAP=acetaminophen; NC=North Carolina; USDA=United States Department of Agriculture; RUCC=Rural-urban continuum code; HPDS=Health Professions Data System; NPPES=National Plan & Provider Enumeration System; Dx=Diagnosis

Table 3.1: Describing dependent and independent variable measures used in dissertation analyses (continued)

Aim	Variable	Type	Time Variation	Data Source	Description
	Independent variables cont'd				
	Lock-in Policy Characteristics				
1,2	Month	Continuous	Variant	Medicaid	Month of study period
1,2	Lock-in period	Dichotomous	Variant	Medicaid	1=Lock-in policy period; 0=Pre-lock-in policy period
1,2	Lock-in period * month	Continuous	Variant	Medicaid	Month of Lock-in policy period
1,2	Lock-in eligible	Dichotomous	Variant	Medicaid	1=Lock-in eligible; 0=Not eligible
1,2	Lock-in enrolled **(KEY IV)**	Dichotomous	Variant	Medicaid	1=Enrolled in lock-in program; 0=Not enrolled
1,2	Lock-in enrolled * month	Continuous	Variant	Medicaid	Month of lock-in enrollment
1,2	Lock-in enroll delay	Dichotomous	Variant	Medicaid	1=Lock-in eligible/not enrolled; 0=Eligible/enrolled or ineligible/not enrolled
1,2	Lock-in enroll delay * month	Continuous	Variant	Medicaid	Month of lock-in eligibility without enrollment
1,2	Opioid-based eligibility	Dichotomous	Invariant	Medicaid	1=Lock-in eligible due to opioid use; 0=Not opioid eligible
1,2	Benzodiazepine-based eligibility	Dichotomous	Invariant	Medicaid	1=Lock-in eligible due to benzodiazepine use; 0=Not benzodiazepine eligible
1,2	Provider-based eligibility (proxy)	Dichotomous	Invariant	Medicaid	1=Four or more unique pharmacies used; 0=Less than four unique pharmacies
1,2	No eligibility	Dichotomous	Invariant	Medicaid	1=No lock-in eligibility criteria met; 0=Any lock-in eligibility met
	Opioid exposure measures				
3	Opioid prescription fills	Continuous	N/A	Medicaid	Number of opioid prescription claims
3	Opioid pharmacies used	Continuous	N/A	Medicaid	Number of unique pharmacies dispensing opioid prescriptions
3	Daily opioid dose	Continuous	N/A	Medicaid	Average daily milligram morphine equivalents received
3	Daily acetaminophen dose	Continuous	N/A	Medicaid	Average daily milligrams of acetaminophen received from opioid combination products

Note: IV=independent variable

3.4.1 Dependent Variables

Aim 1 analyzed two distinct outcome measures that were assessed using the linked Medicaid—Controlled Substances Reporting System dataset. These included:

- A binary indicator of a circumvented fill, defined as the presence of any record for an opioid analgesic or benzodiazepine prescription fill in the CSRS dataset that lacked a corresponding claim in the Medicaid dataset for the same prescription fill. The presence of circumvention was assessed in calendar month intervals.
- A count measure of number of circumvented fills for an individual in a given calendar month.

Aim 2 analyses involved three outcome variables that were measured using the linked Medicaid-CSRS dataset (Table 3.2). Each Aim 2 outcome reflected the potency and abuse potential of prescription opioid products received by NC MLIP enrollees. These included:

- A dichotomous prescription-level measure indicating whether an opioid prescription fill contained a long-acting preparation vs. an immediate-release preparation. Long-acting preparations included extended-release oral formulations and transdermal patch formulations. Immediate release opioid products do not have features that reduce the rate of absorption of opioid products. Classification of long-acting versus short-acting opioid products was performed using a drug information database and expert review.[31]
- A binary prescription-level variable indicating whether an opioid fill was for a Schedule II product vs. a Schedule III-V product, as per DEA classifications. This measure reflected opioid scheduling in use during the study period. Therefore, hydrocodone combination products were assessed as Schedule III products in Aim 2 analyses despite having since been reclassified as Schedule II following the end of the dissertation study period. As of 2014, tramadol products were reclassified as Schedule IV. However, tramadol products were not included in Aim 2 analyses as they were not a controlled substance during the dissertation study period and therefore not regulated under the NC MLIP. Classification of Schedule II opioid products was performed using a drug information database and expert review.[31]

- A continuous prescription-level variable of opioid dose measured as prescribed average daily milligram morphine equivalents (MMEs). MMEs represent the dose of an opioid product standardized to oral morphine, which facilitates direct comparison of dosage across opioid products. Total MMEs provided by a single opioid prescription were calculated by multiplying the prescription quantity dispensed by the drug strength and by the oral morphine equivalent conversion factor. The oral morphine equivalent conversion factor came from evidence-based recommendations from the CDC for calculating equivalent opioid doses.[213,214] Average daily MME for an opioid prescription was calculated by dividing by the total MMEs provided by the prescription divided by prescribed days supply. This measure is the gold standard for assessing opioid exposure levels in the prescription drug abuse literature.[135,140-142] Quantity and days supply values were taken from the adjudicated Medicaid claim for all Medicaid-covered prescriptions and taken from CSRS records for all circumvented fills. There were 0.6% of prescription fills included in Aim 2 analyses in which quantity value discrepancies existed between Medicaid and CSRS data. The Medicaid claim quantity value was used in these instances. Less than 2% of Aim 2 prescription records for circumvented fills reported a days supply of zero in the CSRS record, which was assumed to be in error. For these circumvented fill records, we imputed days supply based on the average day-per-unit dispensed for that specific product, which we calculated from similar prescription fills in the data that had complete quantity and days supply information.

Table 3.2: Categorizations of Schedule II opioids, long-acting opioids, and MME conversion factors

Aim 2 measure	Opioid product
Schedule II opioid agents	Codeine (single agent), fentanyl, hydromorphone, meperidine, methadone, morphine, opium, oxycodone, oxymorphone tapentadol
Long-acting opioid products	Buprenorphine patch, fentanyl patch, hydromorphone ER tabs, methadone tabs/caps/liquid, morphine ER caps/tabs, oxycodone ER tabs, oxymorphone ER tabs, tapentadol ER tabs
MME Conversion Factor	
0.10	Meperidine
0.125	Oral transmucosal fentanyl
0.15	Codeine
0.23	Propoxyphene
0.25	Dihydrocodeine
0.37	Pentazocine
0.40	Tapentadol
1.00	Hydrocodone, morphine
1.50	Oxycodone
3.00	Methadone, oxymorphone
4.00	Hydromorphone
7.00	Butorphanol
7.20	Transdermal fentanyl[1]
12.60	Transdermal buprenorphine[2]

Note: ER=Extended release; Tabs=tablets; Caps=Capsules; MME=Milligram morphine equivalent
1. Conversion factor of transdermal fentanyl was based on the assumption that 1mg parenteral fentanyl = 100mg oral morphine, and one patch delivers dispensed micrograms/hour for a 24 hour period for 3 days.
2. Conversion factor for transdermal buprenorphine assumed 1mg parenteral buprenorphine = 75mg oral morphine, and one patch delivers dispensed micrograms/hour for a 24 hour period for 7 days

Aim 3 examined five relevant substance use-related clinical outcomes defined using International Classification of Diseases, Ninth Revision, Clinical Modification[215] (ICD-9-CM) case definitions in the NC Medicaid claims data to test and validate various measures of high-risk opioid use. These clinical outcomes included:

- Unintentional opioid overdose event identified in the Medicaid claims data using modified ICD-9-CM code definitions developed by Dunn, et. al and Yang, et. al and validated through chart review.[141,161] A subject meeting at least one of two ICD-9-CM case definitions for an unintentional opioid overdose was considered to have experienced this outcome. The first definition characterized a definite unintentional opioid-related poisoning event, and involved the presence of at least one of the following diagnoses: 965.0X, E850.1, or E850.2. The second case definition captured a probable unintentional opioid overdose and included an ICD-9-CM diagnosis of E935.0, E935.1, or E935.2, indicating an opioid-related adverse effect, plus at least one additional diagnosis on the same date for a specific sign or symptom of an opioid overdose event, including mixed acid-balance disorder (276.4), drug-induced mental disorders (292.1,

292.8X), respiratory distress symptoms (486, 496, 518.81, 518.82, 786.03, 786.05, 786.09, 786.52, 799.0X), and/or altered mental status (780.0X, 780.97). These case definitions for unintentional opioid overdose were modified to exclude ICD-9-CM codes indicating self-injurious intent.

- Acetaminophen overdose event was defined as the presence of one of the following ICD-9-CM codes in any diagnosis field in the Medicaid claims data: 965.4, E850.4, or E935.4. The original case definition (which also included E950.0 that was not used in this study due to lack of specificity to acetaminophen) was validated through medical chart abstraction (C-statistic=0.86) by Myers, et al.[216]
- An unintentional overdose event involving any drug product, including alcohol, was identified using a claims-based definition employed by Miller, et al, as well as expert review.[138] The presence of an ICD-9-CM code of 960-980 or E850-E860 was defined as an unintentional overdose event of any drug product, as well as any unintentional opioid or acetaminophen overdose as defined previously.
- The presence of an opioid use disorder was assessed using ICD-9-CM case definitions informed by prior studies from White, et al in 2005 and 2009.[151,217] A subject was considered to have received an opioid use disorder diagnosis if they recorded at least one of the following ICD-9-CM codes in the Medicaid claims data: 304.0X, 304.7X, or 305.5X.
- The presence of any substance use disorder was adapted from White's opioid use disorder case definition[151,217] and included the presence of at least one of the following ICD-9-CM codes: 303.X, 304.X, or 305.X.

3.4.2 Independent Variables

Independent variable measures were categorized into their role as a predisposing, enabling, or need characteristic, as detailed previously in Section 2.4, which described this dissertation's conceptual model based on the Andersen's Behavioral Model of Health Services Use. Independent variables also included NC MLIP characteristics that captured overall policy implementation characteristics and subjects' experience with the program.

3.4.2.1 Predisposing Characteristics

Analyses in all three aims utilized select predisposing characteristics coded using Medicaid data as follows:

- Subject age was defined as a subject's age, in years, on the 15th day of the observed month. In aim 3, age was defined as patient age, in years, at the index opioid fill.
- Sex was coded as a binary indicator with 1 denoting female sex and 0 denoting male sex.
- Race/ethnicity will be coded using mutually exclusive and exhaustive categories of race and ethnicity that were self-reported by subjects at the time of their Medicaid enrollment. The categories include White, Black, and other/unknown. White race serves as the referent group.

3.4.2.2 Enabling Characteristics

Five county-level variables representing enabling characteristics were measured for use as covariates in Aim 1 and 2 analyses.

- Rural/urban residence was assessed using the measure of Rural-Urban Continuum Code (RUCC) developed by the United States Department of Agriculture's (USDA) Economic Research Service.[218] RUCC is a county-level measure with a discrete range of 1-9, with 1 denoting the most metropolitan counties and 9 denoting the most rural counties. The 2013 RUCC measures were used, which were created based on county population and commuting flow data from the American Community Survey. These were linked to a subject's county of residence from the Medicaid data.
- The binary indicator of residence in a metropolitan vs. non-metropolitan county was created based on the USDA's suggested delineation of RUCC codes. Metropolitan counties had a RUCC of 1-3, and a non-metropolitan county has a RUCC of 4-9.
- Prescriber supply was defined as the total number of actively practicing medical professionals with Schedule II through Schedule V prescribing authority (physicians, physician assistants, and nurse practitioners) in a subject's county of residence. This measure was created using North Carolina Health Professions Data System data from 2010.[219] It was linked to study subjects' county of residence in the Medicaid data.
- Pharmacy supply was defined as the number of licensed community and outpatient pharmacies in a subject's county of residence. This measure was derived using the Centers for Medicare and Medicaid Services 2012 master file of pharmacy National Provider Identifiers by identifying the number of pharmacies in each North Carolina county.[220] The pharmacy supply measure was linked to study subjects' county of residence in the Medicaid data.
- The border county measure was a dichotomous indicator for whether a subject's county of residence shared a border with neighboring states. This was assessed to control for potential CSRS data artifacts stemming from the fact that controlled substance fills occurring outside of North Carolina would not be captured in the CSRS. The border county variable accounted for

potential disproportionate missingness of controlled substance service use behavior occurring across state lines owing to closer proximity to state borders.

3.4.2.3 Need Characteristics

Multiple variables were created using Medicaid claims data to indicate the presence of key diagnoses in which either opioids and benzodiazepines are indicated or for which the diagnosis is a known risk factor for nonmedical controlled substance use. These included chronic noncancer pain, anxiety disorder, substance use disorder, depression, and any other mental health disorder. Indicator variables for each condition reflected the presence of at least one ICD-9-CM diagnosis code in the Medicaid claims data during the 12-month baseline study periods of Aims 1 and 2 using coding groups detailed in Table 3.2. The chronic noncancer pain diagnosis codes were identified based on prior literature and expert review.[221,222] Diagnosis codes for the anxiety, substance use, depression, and other mental health disorder were identified using the Agency for Healthcare Research & Quality's Clinical Classification Software and expert review.[223]

Table 3.3: ICD-9-CM diagnosis code groups for need characteristic indicator variables

Need variable	ICD-9-CM diagnosis codes
Chronic noncancer pain	Chronic pain: 3382 33821 33822 33828 33829 3384; Back pain: 7213-7219 7222 72230 72270 72280 72290 72232 72272 72282 72292 72233 72273 72283 72293 724 7371 7373 7384 7385 7392 7393 7394 75610 75611 75612 75613, 75619 8054 8058 8392 83942 846 8460 8471 8473 8472 8479; Neck pain: 7210 7211 7220 72231 72271 72281 72291 723 8390 8391 8470; Arthritis: 710-719 725-739; Headache and migraine: 346 30781; HIV/AIDS: 042 07953 27910 27919 79571 V08
Anxiety disorder	29384 30000 30001 30002 30009 30010 30020 30021 30022 30023 30029 3003 3005 30089 3009 3080 3081 3082 3083 3084 3089 30981 3130 3131 31321 31322 3133 31382 31383
Substance use disorder	Alcohol: 2910 2911 2912 2913 2914 2915 2918 29181 29182 29189 2919 30300 30301 30302 30303 30390 30391 30392 30393 30500 30501 30502 30503 3575 4255 53530 53531 5710 5711 5712 5713 76071 9800 Other substances: 2920 29211 29212 2922 29281 29282 29283 29284 29285 29289 2929 30400 30401 30402 30403 30410 30411 30412 30413 30420 30421 30422 30423 30430 30431 30432 30433 30440 30441 30442 30443 30450 30451 30452 30453 30460 30461 30462 30463 30470 30471 30472 30473 30480 30481 30482 30483 30490 30491 30492 30493 30520 30521 30522 30523 30530 30531 30532 30533 30540 30541 30542 30543 30550 30551 30552 30553 30560 30561 30562 30563 30570 30571 30572 30573 30580 30581 30582 30583 30590 30591 30592 30593 64830 64831 64832 64833 64834 65550 65551 65553 76072 76073 76075 7795 96500 96501 96502 96509 V6542
Depression	29620 29621 29622 29623 29624 29625 29626 29630 29631 29632 29633 29634 29635 29636 3004 3091 311
Other mental health	Adjustment disorders: 3090 3091 30922 30923 30924 30928 30929 3093 3094 30982 30983 30989 3099 ADHD-related disorders: 31200 31201 31202 31203 31210 31211 31212 31213 31220 31221 31222 31223 3124 3128 31281 31282 31289 3129 31381 31400 31401 3141 3142 3148 3149 Delirium/Dementia: 2900 29010 29011 29012 29013 29020 29021 2903 29040 29041 29042 29043 2908 2909 2930 2931 2940 2941 29410 29411 29420 29421 2948 2949 3100 3102 3108 31081 31089 3109 3310 3311 33111 33119 3312 33182 797 Developmental disorders: 3070 3079 31531 31534 31535 31539 V401 31501 31502 31509 31532 3155 3158 317 3180 3181 3182 319 31500 3151 3152 3159 V400 3154 29900 29901 29910 29911 29980 29981 29990 29991 30720 30721 30722 30723 Impulse control: 31230 31231 31232 31233 31234 31235 31239 Bipolar disorders: 29600 29601 29602 29603 29604 29605 29606 29610 29611 29612 29613 29614 29615 29616 29640 29641 29642 29643 29644 29645 29646 29650 29651 29652 29653 29654 29655 29656 29660 29661 29662 29663 29664 29665 29666 2967 29680 29681 29682 29689 29690 29699 Personality disorders: 3010 30110 30111 30112 30113 30120 30121 30122 3013 3014 30150 30151 30159 3016 3017 30181 30182 30183 30184 30189 3019 Schizophrenia/Psychosis: 29381 29382 29500 29501 29502 29503 29504 29505 29510 29511 29512 29513 29514 29515 29520 29521 29522 29523 29524 29525 29530 29531 29532 29533 29534 29535 29540 29541 29542 29543 29544 29545 29550 29551 29552 29553 29554 29555 29560 29561 29562 29563 29564 29565 29570 29571 29572 29573 29574 29575 29580 29581 29582 29583 29584 29585 29590 29591 29592 29593 29594 29595 2970 2971 2972 2973 2978 2979 2980 2981 2982 2983 2984 2988 2989 Sleep disorder: 30740 30741 30742 30743 30744 30745 30746 30747 30748 30749 Other: 33392 V110 V111 V112 V114 V118 V119 V154 V1541 V1542 V1549 V1582 V6285 V663 V701 V702 V7101 V7102 V7109 V790 V792 V793 V798 V799 30012 30013 30014 30015 3006 3071 30750 30751 30752 30753 30754 30759 30016 30019 3060 3061 3062 3063 3064 30650 30652 30653 30659 3066 3067 3068 3069 3021 3022 3023 3024 30250 30251 30252 30253 3026 30270 30271 30272 30273 30274 30275 30276 30279 30281 30282 30283 30284 30285 30289 3029 30651 30011 3007 30081 30082 30780 30781 30789 29389 2939 3101 316 64840 64841 64842 64843 64844 V402 V403 V4031 V4039 V409 V673

Note: ICD-9-CM=International Classification of Diseases, 9th revision, Clinical Modification; HIV=Human immunodeficiency virus; AIDS=Acquired immune deficiency syndrome; ADHD=Attention deficit hyperactivity disorder

In addition, we created two measures of overall comorbid disease burden using Medicaid claims data.

- The Charlson Comorbidity Index score was calculated for each study subject in Aims 1 and 2 to capture overall comorbidity burden and baseline health status. The Charlson Comorbidity Index was originally developed to predict one-year mortality and involves identifying the presence of 17 unique clinical conditions diagnoses in a patient.[224] Each condition is assigned a point value weighted by severity, and scores can range from 0 to 37 with higher scores indicating greater comorbid burden. The Charlson score was measured using Medicaid claims over the 12-month baseline observation period in Aims 1 and 2 using ICD-9-CM coding schemes validated by Quan, et al in 2005.[225] It is important to note that the pain, mental health, and substance abuse disorders captured in the binary variables described previously did not contribute to the Charlson Comorbidity Index score.
- We also used Medicaid claims data to measure the number of unique prescription medications, at the drug product level, filled by a study subject over the 12-month baseline period in Aims 1 and 2 analyses. This measure of prescription drug burden has been previously validated as a strong independent predictor of a patient's comorbid burden and overall clinical complexity.[226]

3.4.2.4 Lock-in Policy Variables

Multiple independent variables were also developed to capture characteristics of the North Carolina Medicaid lock-in program implementation and subjects' eligibility and enrollment in the program. We used Medicaid data from North Carolina DMA to construct the following measures:

- The month variable measured time across the entire study periods of Aims 1 and 2 in calendar month intervals, with Month 1 referring to October 2009—one year prior to MLIP implementation—through Month 36, representing September 2012.
- Lock-in period was a binary indicator of NC MLIP operation, with 1 referring to the active lock-in policy period starting October 2010 and 0 reflecting the pre-policy period before October 2010.
- Lock-in period*month was an interaction variable that measured the discrete number of months into the lock-in policy period being observed, with 1=October 2010 through 24=September 2012.
- Lock-in eligibility was assessed monthly with dichotomous variables indicating whether a subject had seven or more opioid prescriptions; seven or more benzodiazepine prescriptions; or four or more unique opioid and benzodiazepine dispensing pharmacies in a two calendar month period in Medicaid claims data (see provider-based MLIP eligibility measure definition below for further detail about the pharmacy use measure). October 2010 was the first month in which lock-in eligibility was possible, because this was when the program was implemented. The first two-

month period in which lock-in eligibility was assessed was July/August 2010. A subject was considered perpetually eligible for the MLIP once they met at least one eligibility criterion, which reflected the program administrator's consideration of MLIP eligibility, necessitated by the phased-in program implementation.

- Lock-in enrollment represented the key independent variable in Aims 1 and 2 and was defined as a monthly binary indicator variable in which 1=enrolled in the MLIP at any point in the calendar month and 0=not enrolled in the MLIP.
- The interaction term, lock-in enrollment*month, was a continuous measure of the number of months into a subject's lock-in enrollment period, with 1=first month enrolled in the MLIP.
- The lock-in enrollment delay variable was defined dichotomously as 1=eligible for the MLIP but not enrolled in a given month and 0=eligible for and enrolled in the MLIP or ineligible and not enrolled in the MLIP. This variable accounted for the fact that the NC MLIP implementation was phased in, and subjects with the highest controlled substance use based on retrospective claims/manual review were prioritized for enrollment. Therefore, many subjects were initially eligible for the MLIP but experienced a delay in enrollment.
- The lock-in enrollment delay*month interaction variable was a monthly measure of the number of months in which an eligible subject's MLIP enrollment was delayed. This variable had a value of 0 prior to meeting MLIP eligibility, had a consecutively discrete positive value during the delay period, and returned to 0 once enrolled in the MLIP.
- Opioid-based eligibility was a fixed measure defined dichotomously as 1=eligible for the MLIP due to recording seven or more opioid claims in a two calendar month period and 0=not eligible based on opioid use. Eligible opioid prescriptions included all products assessed by NC MLIP administrators (First DataBank therapeutic class codes: H3A, H3H, H3J, H3M, H3N, H3U, and H3X, excluding tramadol products with generic code numbers of 07221, 26387, 50417, 50427, 13909, and 99151).[227]
- Benzodiazepine-based eligibility was a fixed measure defined dichotomously as 1=eligible for the MLIP due to having seven or more benzodiazepine claims in a two calendar month period and 0=not eligible based on benzodiazepine use.
- Provider-based MLIP eligibility was approximated using the dichotomous measure of 1=receipt of opioid and/or benzodiazepine paid Medicaid claims from four or more unique community and outpatient pharmacies in a two calendar month period and 0=less than four unique pharmacies used to obtain these medications. It must be noted that the measure of unique dispensing pharmacies was not used in practice to assess NC MLIP eligibility; NC MLIP administrators used an eligibility measure of four or more unique prescribers of these medications. The data provided

by program administrators did not allow for reliable assessment of the number of unique prescribers. Therefore, we constructed the measure of number of unique community and outpatient pharmacies used to obtain opioids and benzodiazepines in the Medicaid claims data as a proxy measure for prescriber use, because it similarly captured the extent of provider use.

- No MLIP eligibility was defined as 1=enrolled in the MLIP despite never previously satisfying any of the three previous MLIP eligibility criteria and 0=meeting at least one MLIP eligibility criterion prior to MLIP enrollment.

3.4.2.5 Opioid Utilization Measures

The final set of independent variables represented varied measures of opioid exposure used as key independent variables in Aim 3 to predict relevant prescription drug-abuse related clinical outcomes. All opioid utilization measures were constructed in Medicaid claims data and included:

- The number of opioid prescription fills, defined as the number of paid Medicaid claims for opioid analgesic products for a single study subject in a 60-day observation period.
- The measure of number of opioid-dispensing pharmacies was defined as the discrete number of community and outpatient pharmacies that dispensed a Medicaid-covered opioid analgesic prescription to a single study subject in a 60-day observation period.
- Average daily opioid dosage was defined as the average MMEs of opioid products obtained through NC Medicaid for the 60-day observation period. MMEs were calculated by multiplying the prescription quantity by the drug strength in milligrams and then multiplying this total by the appropriate morphine equivalent conversion factor specific to that opioid agent.[213,214] MMEs were then summed across a 60-day period and divided by 60 to obtain average daily opioid exposure in MMEs.
- Cumulative acetaminophen dosage was defined as the average daily milligrams of acetaminophen received over a 60-day period by a study subject through Medicaid-covered prescriptions for combination opioid-APAP drug products.

3.5 DATA ANALYSIS BY AIM

3.5.1 Aim 1

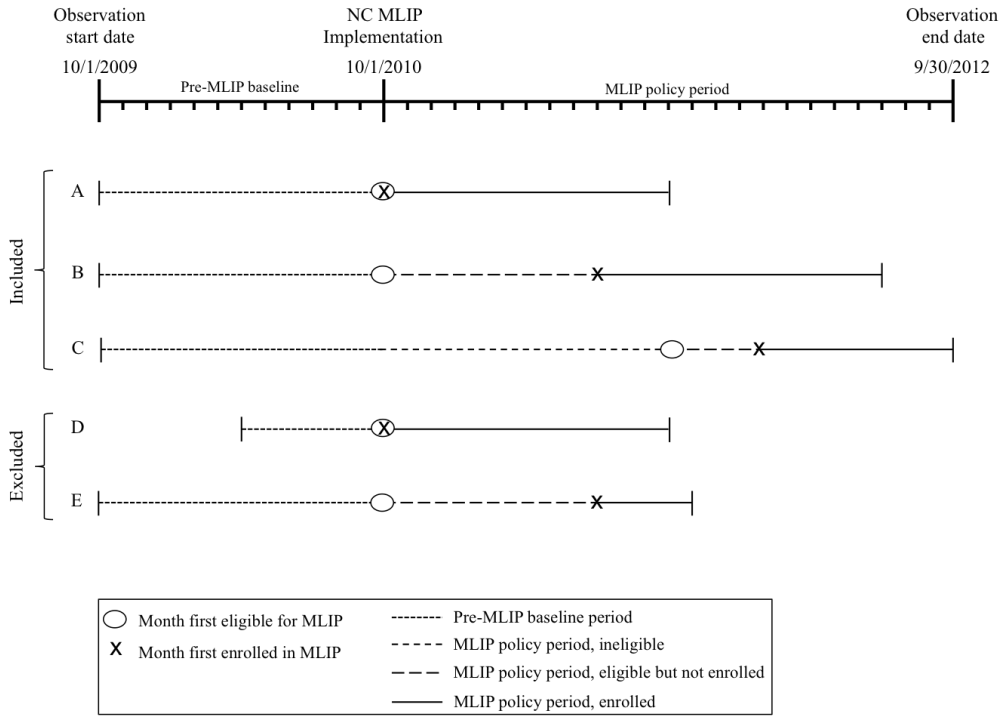
To examine the effect of the North Carolina Medicaid Recipient Management Lock-in Program, as well as patient-level characteristics, on controlled substance circumvention behaviors.

3.5.1.1 Study Design—Aim 1

We employed a retrospective cohort study design with repeated monthly measures in a longitudinal cohort of continuously enrolled NC Medicaid beneficiaries to investigate the effect of enrollment in the MLIP and patient-level characteristics on controlled substance circumvention. The study period for analysis ranged from 10/1/2009 through 9/30/2012, representing one year before through two years following MLIP implementation on October 1, 2010. The Aim 1 study sample consisted of a single cohort of NC Medicaid beneficiaries enrolled in the Medicaid lock-in program within the first 18 months of program implementation. Subjects were also continuously enrolled in NC Medicaid for twelve months prior to MLIP implementation through at least six months following their MLIP enrollment to allow for longitudinal analysis.

This retrospective cohort design facilitated observation of NC MLIP enrollees' circumvention behaviors through up to four distinct phases of the MLIP policy (Figure 3.1). Each subject had a mandatory 12-month baseline period leading up to MLIP policy implementation in which to observe circumvention prior to the program's existence and to assess baseline covariates. We required subjects to contribute data for at least six months of their 12-month MLIP enrollment period for observation of the effect of MLIP enrollment on circumvention. Subject A in Figure 3.1 represents an individual with a 12-month pre-MLIP baseline period that was eligible and enrolled in the NC MLIP at the program's start in October 2010 and contributed a full 12 months of data for their entire initial MLIP enrollment period.

Figure 3.1: Aim 1 retrospective cohort study design



There were two distinct observation periods in addition to the pre-MLIP implementation baseline period and MLIP enrollment period that reflected the potential for the MLIP to have had an indirect effect on controlled substance-seeking behaviors among those not yet enrolled in the program. Due to the phased-in implementation of the NC MLIP, many study subjects experienced a period of delayed enrollment after first becoming eligible. This enrollment delay period is demonstrated in Subject B in Figure 3.1 who was eligible for MLIP enrollment at program implementation in October 2010 but whose enrollment was delayed nine months. Lastly, subjects may not have become eligible for MLIP enrollment until after the program was implemented, creating a period of observation in which the MLIP was active but a subject was not yet eligible or enrolled. Subject C depicts an individual who first became eligible for the MLIP 12 months into the program's existence and then had a four-month delay in enrollment.

In figure 3.1, excluded subjects D and E are shown to further demonstrate the Aim 1 study design, in which we required a 12-month pre-MLIP baseline observation period (Subject D) and at least six months of observation after they were enrolled in the MLIP (Subject E).

3.5.1.2 Study Cohort—Aim 1

The study cohort initially included all NC Medicaid beneficiaries enrolled in the MLIP during the entire study period of 10/1/2009 through 9/30/2012. We then reduced the sample to NC MLIP enrollees that first entered the program during the first 18 months of the NC MLIP policy period from 10/1/2010 to 3/31/2012. The sample was further restricted to subjects with 12 months of continuous Medicaid coverage prior to NC MLIP implementation in October 2010 and continuing through at least six months following their lock-in date. Lastly, we excluded subjects who were less than 18 or greater than 65 years of age at any point in their observation period.

The continuous Medicaid enrollment inclusion requirements ensured we were able to observe baseline circumvention behaviors for a full year prior to the existence of the NC MLIP. It also allowed for baseline assessment of need characteristic variables. The post-MLIP enrollment continuous coverage requirement ensured we were able to observe subjects' circumvention behaviors for at least six months following lock-in. Aim 1 subjects could have contributed up to 12 months of data following enrollment in the MLIP, which is the length of the initial lock-in period, provided their observation in the data wasn't censored by a gap in Medicaid coverage or the end of the study period on 9/30/2012.

Continuous Medicaid enrollment was defined as having gaps in coverage of no greater than one calendar month. We examined coverage gaps in the final analytic cohort to assess the level of turbulence in NC Medicaid coverage. High levels of turbulence would likely bias study estimates through inclusion of monthly observations of controlled substance use behaviors that was assumed to occur in the context of Medicaid coverage that did not actually exist. However, 93% of the final sample had zero gap months of coverage, and the maximum number of gap months was two (Appendix Table 2). This level of Medicaid coverage turbulence was within the scope of commonly used definitions of continuous Medicaid coverage that allow one month of coverage gap for every 12 months of observation.[228,229] A sensitivity analysis was performed in which Aim 1 models were ran excluding the 7% of subjects that had a gap in NC Medicaid coverage (Appendix Table 3). Differences in findings between the sensitivity and base analyses were negligible, so we reported findings for the base Aim 1 cohort.

3.5.1.3 Statistical Analyses—Aim 1

We used descriptive statistics to summarize the Aim 1 cohort. We reported means and frequencies of the predisposing, enabling, and need characteristics detailed previously in Section 3.4, both overall and by route of MLIP eligibility. We also described MLIP policy characteristics of the study sample, including frequencies of routes of MLIP eligibility and months of observation in various policy phases, such as MLIP enrollment delays. Bivariate analyses were performed to compare opioid and benzodiazepine utilization behaviors—both Medicaid-covered and circumvented—before and after MLIP enrollment. T-tests and chi-square tests were performed for continuous and binary measures, respectively, with statistical significance defined with an alpha level of 0.05.

We used generalized estimating equations (GEE) to model the effect of enrollment in the NC MLIP and patient predictors on circumvention behaviors. GEE is an extension of the generalized linear model and estimates a population average effect of independent variables on an outcome while accounting for correlation across repeated longitudinal measures.[230] GEE requires specification of a distribution family of the outcome variable, a link function—which serves to linearize non-linear relationship between independent and dependent variables—, and a correlation structure across repeated measures.

The Aim 1 analytic dataset was structured to allow for GEE modeling by measuring time-varying variables in calendar month increments. The study observation period began with October 2009 identified as Month 1 and extended through two years following MLIP implementation with September 2012 characterized as Month 36. Therefore, study subjects contributed a minimum of 18 data observations (monthly measures from October 2009 – March 2011) to a maximum of 36 observations (monthly measures from October 2009 – September 2012), depending on when they were enrolled in the program and continuity of Medicaid coverage. Limitations of the Medicaid-CSRS dataset did not allow for identification of a comparator group of controlled substance users never enrolled in the MLIP. However, the GEE repeated measures design allowed for the single MLIP enrollee cohort to, in a sense, serve as its own control. Most of the MLIP enrollees experienced a delay in enrollment due to a phasing in of the

policy, so observing these subjects' circumvention behaviors while they qualified for MLIP enrollment for a period of time before they were actually enrolled served a pseudo-control group. Additionally, the within-individual control approach we used may be preferred, because potential control subjects not chosen for enrollment in the MLIP may not be an appropriate comparator to MLIP enrollees.

We performed two GEE models to estimate the effect of the dichotomous indicator of MLIP enrollment—the key independent variable—and patient-level characteristics on the likelihood of obtaining any circumvented fill and on the number of circumvented fills received in a person-month observation. Each GEE model provided distinct, but interesting information about circumvention behaviors in the NC MLIP; the first model examined predictors of engaging in controlled substance circumvention at all, while the second model examined predictors of the number of circumvention events in a month.

The first GEE model used a modified Poisson regression approach to estimate the effect of the MLIP on the likelihood of any circumvented fills in a month. The modified Poisson model allows estimation of relative risk for binary outcome variables through specification of a Poisson distribution family and a log link. Huber/White robust sandwich variance estimators are used to correct artificially wide confidence intervals that are initially produced when fitting a Poisson distribution to the binomially distributed outcome variable. Model estimates are exponentiated to report relative risk. Prior literature has demonstrated the modified Poisson approach is a reliable and efficient estimator of relative risk for binary outcomes in generalized linear models and GEE models with correlated data.[231-233] It provided a number of distinct advantages over the standard logistic regression approach. First, odds ratios estimated with logistic regression always overestimate the association of the independent and dependent variables away from the null, especially when the outcome is common (>10%). Relative risks are a more accurate and conservative estimator. Second, the interpretation of relative risk is naturally much more intuitive than interpretation of the odds ratio. Lastly, the modified Poisson approach is more robust to omitted variable bias than logistic regression. Omitted variable bias affects the actual point estimates in logistic regression as opposed to simply increasing the error term in the model. A sensitivity analysis was performed in

which the dichotomous circumvention outcome measure was modeled with a logistic regression approach to demonstrate odds ratio inflation (Appendix Table 4). The odds ratio on the key MLIP enrollment variable suffered from a relative inflation of 68% over the reported relative risk measure.

The second model used a Poisson count model approach to predict the number of circumvention events in a month. In this GEE model, we specified a Poisson distribution and a log link, and we exponentiated model estimates to report incidence rate ratios. In both GEE models, we specified an autoregressive correlation structure with a lag of one month. Selection of the one month autoregressive correlation structure was guided by the quasi-likelihood information criteria (QIC) method, which indicated this correlation structure provided a better model fit over autoregressive correlations with independent, exchangeable, and unstructured correlations.[234] Robust standard errors—also known as Huber-White sandwich estimators—were used in both GEE models. Robust standard errors in GEE serve two primary purposes in addition to their necessity in the modified Poisson for binary outcomes. First, they produce valid standard errors even in the presence of a misspecified correlation structure.[235] They also account for within-person correlation in GEE by effectively clustering by subject. This prevents artificially small standard errors that would overstate covariate statistical significance.

In addition to the key independent variable of MLIP enrollment, both GEE models controlled for lock-in policy characteristic covariates defined in Section 3.4.2. These measures adjusted for the overall effect of the policy period, delays in MLIP enrollment, and the effects of time spent in various phases of the MLIP policy period. The models also included patient predisposing, enabling, and need characteristic variables as defined previously. The evidence-based conceptual model detailed in Section 2.4.2 guided selection of patient-level variables. The final GEE analytic models are depicted in Figure 3.2.

Figure 3.2. Specification of the Aim 1 generalized estimating equation models

Model 1 (Binary circumvention): Distribution=Poisson, link=log, corr=autoregressive (1 month)
Model 2 (Count circumvention): Distribution=Poisson, link=log, corr=autoregressive (1 month)

Circumvention outcome = $\beta_0 + \beta_1 X_{\text{MLIP enrollment}} + \beta_2 X_{\text{MLIP enrollment*month}} + \beta_3 X_{\text{MLIP delay}} + \beta_4 X_{\text{MLIP delay*month}} + \beta_5 X_{\text{month}} + \beta_6 X_{\text{MLIP period}} + \beta_7 X_{\text{MLIP period*month}} + \beta_8 X_{\text{MLIP eligibility:opioid}} + \beta_9 X_{\text{MLIP eligibility:benzo}} + \beta_{10} X_{\text{MLIP eligibility:provider}} + \beta_{11} X_{\text{MLIP eligibility:none}} + \beta_{12} X_{\text{Age}} + \beta_{13} X_{\text{Female}} + \beta_{14} X_{\text{Black}} + \beta_{15} X_{\text{Other/unknown race}} + \beta_{16} X_{\text{Metropolitan county}} + \beta_{17} X_{\text{Pharmacy supply:11-25}} + \beta_{18} X_{\text{Pharmacy supply:26-50}} + \beta_{19} X_{\text{Pharmacy supply 51-100}} + \beta_{20} X_{\text{Pharmacy supply:>100}} + \beta_{21} X_{\text{Border county}} + \beta_{22} X_{\text{Chronic pain}} + \beta_{23} X_{\text{Anxiety}} + \beta_{24} X_{\text{Substance use}} + \beta_{25} X_{\text{Depression}} + \beta_{26} X_{\text{Other mental illness}} + \beta_{27} X_{\text{Charlson:1}} + \beta_{28} X_{\text{Charlson:}\geq 2} + \beta_{29} X_{\text{Need}} + \beta_{30} X_{\text{Prescription burden}} + \varepsilon$

The final GEE models reflected a few key modifications to the initial patient-level variable specifications. Specifically, county-level prescriber supply was excluded in final analysis due to high correlation with the measure of county-level pharmacy supply upon examination of Pearson's Correlation Coefficients within enabling and need variable groups (r^2=0.92) (Appendix Tables 5 and 6). We also opted to control for residence in a rural county with the dichotomous metropolitan vs. non-metropolitan county indicator as opposed to the ordinal measure of county-level RUCC score to enhance interpretability. Continuous measures of county-level pharmacy supply and Charlson Comorbidity Index score were transformed into categorical variables in the final model to allow for more meaningful interpretation of model output. County pharmacy supply was categorized into 0-10, 11-25, 26-50, 51-100, and >100 pharmacies (Appendix Table 7). Charlson scores were grouped into 0, 1, and ≥2 based on prior literature to reflect no, low, or high comorbidity burden.[236,237] Sensitivity analyses in which these three variables were entered into the GEE models in their original continuous form confirmed that our final analytic models were robust to these categorical transformations (Appendix Table 8).

3.5.2 Aim 2

To investigate prescription-level characteristics of opioid analgesics obtained by North Carolina Medicaid Recipient Management Lock-In Program enrollees through circumvention.

3.5.2.1 Study Design—Aim 2

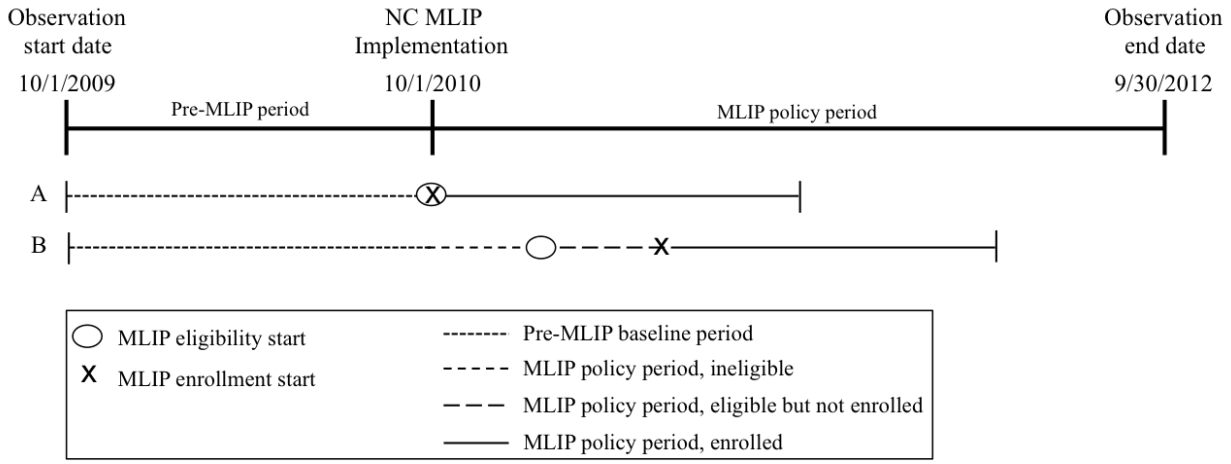
A retrospective cohort study was used to investigate the effect of NC MLIP enrollment, as well as patient-level predictors, on three prescription-level opioid utilization characteristics associated with

increased potential to contribute to abuse and overdose events. The study period for Aim 2 was 10/1/2009 through 9/30/2012, representing one year prior and two years following the start of the NC MLIP. Aim 2 utilized the same study cohort as Aim 1. These subjects represented adult NC Medicaid beneficiaries enrolled in the NC MLIP during its first 18 months of operation. They had continuous NC Medicaid coverage from 10/1/2009 through at least six months following their MLIP enrollment date. Because Aim 2 analyses only investigated opioid use, we further excluded subjects who solely used benzodiazepines during the study period.

The three key prescription-level dependent variables of interest in Aim 2 were a binary indicator of a long-acting versus short-acting opioid prescription fill, a binary indicator of a Schedule II versus Schedule III-V opioid prescription fill, and a continuous measure of average daily prescribed opioid dose in a given prescription, measured in MMEs. We employed a pre-post design to examine changes in these prescription-level characteristics of opioids obtained by NC MLIP enrollees (Figure 3.3). A subject's MLIP enrollment date served as the index date delineating the pre-MLIP enrollment and post-MLIP enrollment periods. The unit of analysis for assessing these outcomes was the prescription fill.

We were primarily interested in observing changes in prescription-level measures of opioid abuse potential for prescriptions obtained through circumvention. This provided valuable information regarding the potential attractiveness of certain opioid prescriptions to circumvention among MLIP enrollees. Additionally, it allowed us to gauge the level of high-risk opioid use that occurred through circumvention, which was previously unobservable for NC MLIP administrators. This knowledge, coupled with observable trends in Medicaid-paid opioid prescriptions provided a previously unseen comprehensive view of changes in prescription-level opioid use behaviors that occurred among MLIP enrollees.

Figure 3.3: Aim 2 pre-post retrospective cohort design for prescription-level outcomes



Retaining the longitudinal cohort from Aim 1 allowed us to assess if a given observation occurred during one of four potential policy phases described in more detail previously (Section 3.5.1.1): pre-MLIP baseline period prior to 10/1/2010; post-MLIP implementation but not yet MLIP eligible; MLIP eligible but not yet enrolled; and enrolled in MLIP. Hypothetical subject B in Figure 3.3 depicts the varying policy phases in which observations could have been made. This enabled us to control for the phased-in policy implementation that resulted in numerous subjects experiencing a delay in MLIP enrollment after meeting the state's definition of high-risk controlled substance use behavior. The Aim 1 cohort, which had continuous NC Medicaid coverage, also ensured a standard baseline observation period in which to construct patient-level clinical need variables known to predict prescription drug abuse behaviors.

3.5.2.2 Study Cohort—Aim 2

Aim 2 analyses used a longitudinal cohort of NC MLIP enrollees stemming from the cohort created in Aim 1 (see Section 3.5.1.2). This cohort included all NC Medicaid beneficiaries that were enrolled the NC MLIP at some point between 10/1/2010 and 3/31/2012. Subjects were continuously enrolled as NC Medicaid beneficiaries from 10/1/2009 through at least six months following their NC MLIP enrollment date. Subjects were excluded if they were less than 18 years or greater than 64 years of age at any point in their observation period. In addition to the exclusion criteria applied to the cohort for Aim 1 analyses, subjects lacking any opioid use during the study period were excluded from Aim 2

analyses. Subjects contributed data until censored either by the end of the study period on 9/30/2012, a lapse in NC Medicaid coverage, or the end of the 12-month NC MLIP enrollment period.

Application of the continuous NC Medicaid coverage inclusion criteria was described previously in Aim 1 (Section 3.5.1.2). Similar concerns persisted in Aim 2 regarding the potential biasing effect of including subjects with one or more gaps in coverage of one month. Roughly 93% of subjects had no lapses in Medicaid coverage. Sensitivity analyses were performed for Aim 2 models among circumvented opioid prescriptions excluding 117 subjects who had one or two month-long gaps in coverage to assess robustness of Aim 2 findings with regard to NC Medicaid coverage turbulence (Appendix Table 9). These sensitivity analyses showed a negligible impact in observed relative risk estimates for the binary schedule II opioid and long acting opioid outcomes, as well as negligible changes in marginal effect estimates for the continuous mean prescribed MME/day outcome. Therefore, no further concern persisted over a biasing effect of NC Medicaid coverage turbulence in the Aim 2 cohort, and primary analysis findings in the full Aim 2 cohort are presented.

3.5.2.3 Statistical Analyses—Aim 2

Descriptive statistics for patient-level characteristics of the study cohort, including predisposing, enabling, and need variables, were conducted in Aim 1. In Aim 2, we examined prescription-level descriptive characteristics of opioid prescriptions received by study subjects. These include frequencies of the primary outcome variables of long-acting opioid and Schedule II opioid fills, and mean values for average daily MMEs. Additionally, we further described opioid prescription characteristics, including the frequencies of individual opioid agents received (hydrocodone product, oxycodone product, etc.) and specific opioid product formulations received (hydrocodone/acetaminophen 5mg/325mg tablets, Duragesic 50mcg/hour patches, etc.). All opioid prescription-level descriptive statistics were reported for the circumvented opioid prescription fills, Medicaid-covered opioid fills, and the entire sample of opioid prescriptions from both payment sources.

Bivariate analyses were performed to compare differences in opioid prescription-level characteristics before and after subject enrollment in the NC MLIP. Bivariate comparisons were reported for circumvented opioid prescription fills, as well as for the Medicaid-covered subset of opioid prescriptions and total opioid prescription fills. Chi-squared tests examined differences between dichotomous measures before and after MLIP enrollment. Paired T-tests were performed to compare means of continuous measures. Statistical significance was defined at an alpha level of 0.05.

Generalized linear models (GLM) were used to estimate the effect of the key independent variable—a binary indicator of NC MLIP enrollment—and patient characteristics on the three key outcome measures: the likelihood of a long-acting opioid prescription fill, the likelihood of a Schedule II opioid prescription fill, and the average daily MME prescribed. The unit of analysis was at the opioid prescription-level. GLM is a highly flexible class of models that allows researchers to specify the variance distribution and a link function that linearizes non-linear relationships between independent and dependent variables.[238,239] The GLM models investigating binary outcomes employed a modified Poisson regression approach to estimate relative risks. The modified Poisson regression approach involved specification of a Poisson distribution family and log link. Huber/White sandwich variance estimators were necessary in the modified Poisson model to correct inappropriately wide confidence intervals initially produced when fitting a Poisson distribution to the binary outcome. Specifically, we used cluster-robust sandwich estimators to account for within-subject correlation. Model estimates were exponentiated to report relative risks. The modified Poisson approach is a reliable and efficient estimator of relative risk for dichotomous outcomes.[231,232] It is often preferred over the logistic regression model due to the relative risk's improved accuracy when estimating common outcomes, more intuitive interpretation compared to the odds ratio, and enhanced robustness to omitted variable bias over logistic regression.

GLM models predicting the continuous average daily MME outcome used an inverse Gaussian distribution and a log link. This distribution and link function were selected based on examination of the outcome distribution and relevant specification tests for the key model of circumvented opioid fills. The average MME/day outcome variable responses, as well as residuals from ordinary least squares modeling

of the level outcome, exhibited a strong right skew (Appendix Figure 2), suggesting the appropriateness of the logged form of the dependent variable. A Modified Park Test found that an inverse Gaussian distribution family with a log link provided the best model fit.[240] This was verified through a Pregibon's link test, which indicated appropriate model specification[241,242], and a normal distribution of plotted residuals from the GLM model with inverse Gaussian distribution and log link (Appendix Figure 3). Cluster-robust standard errors were used to account for within-subject correlation and enhance robustness of the model output in the face of possible misspecification. We reported the average differential/marginal effects of independent variables on average daily MME dose per prescription. Prescription opioid fills for injectable solutions, powder, and suppository formulations were excluded from the GLM analysis of average daily MMEs. This was necessary due to an inability to reliably calculate MME values for these dosage forms. Excluding these products from MME analysis is common practice[135,142,213], and it resulted in dropping only 0.13% of opioid prescription fills.

Aim 2 GLM models controlled for the patient-level and policy-level covariates included in Aim 1 analyses of circumvention behavior (Figure 3.4). Selection of patient predisposing, enabling, and need characteristic variables was driven by the evidence-based conceptual model described in Section 2.4.2. The policy covariates controlled for time trends, the various phases of policy implementation, and route of NC MLIP eligibility. Variable specifications in Aim 2 base analyses reflected those employed in Aim 1 models. Each of the GLM models were performed in the sample of circumvented opioid prescription fills, as well as in the sample of Medicaid-covered opioid prescription fills and combined sample of all opioid fills. This allowed observation of changes in the opioid characteristic outcomes attributable to circumvention behavior, while placing these changes in the overall context of opioid utilization from all payment sources.

Figure 3.4: Specification of Aim 2 generalized linear models

GLM (Long-acting opioid fill): Distribution=Poisson, link=log, cluster-robust standard errors
GLM (Schedule II opioid fill): Distribution=Poisson, link=log, cluster-robust standard errors
GLM (Average daily MME received): Distribution=Inverse Gaussian, link=log, cluster-robust standard errors

Model covariate specifications = $\beta_0 + \beta_1 X_{\text{MLIP enrollment}} + \beta_2 X_{\text{MLIP enrollment*month}} + \beta_3 X_{\text{MLIP delay}} + \beta_4 X_{\text{MLIP delay*month}} + \beta_5 X_{\text{month}} + \beta_6 X_{\text{MLIP period}} + \beta_7 X_{\text{MLIP period*month}} + \beta_8 X_{\text{MLIP eligibility:opioid}} + \beta_9 X_{\text{MLIP eligibility:benzo}} + \beta_{10} X_{\text{MLIP eligibility:provider}} + \beta_{11} X_{\text{MLIP eligibility:none}} + \beta_{12} X_{\text{Age}} + \beta_{13} X_{\text{Female}} + \beta_{14} X_{\text{Black}} + \beta_{15} X_{\text{Other/unknown race}} + \beta_{16} X_{\text{Metropolitan county}} + \beta_{17} X_{\text{Pharmacy supply:11-25}} + \beta_{18} X_{\text{Pharmacy supply:26-50}} + \beta_{19} X_{\text{Pharmacy supply 51-100}} + \beta_{20} X_{\text{Pharmacy supply:>100}} + \beta_{21} X_{\text{Border county}} + \beta_{22} X_{\text{Chronic pain}} + \beta_{23} X_{\text{Anxiety}} + \beta_{24} X_{\text{Substance use}} + \beta_{25} X_{\text{Depression}} + \beta_{26} X_{\text{Other mental illness}} + \beta_{27} X_{\text{Charlson:1}} + \beta_{28} X_{\text{Charlson:}\geq 2} + \beta_{29} X_{\text{Need}} + \beta_{30} X_{\text{Prescription burden}} + \varepsilon$

3.5.3 Aim 3

To identify and validate the most effective measures of high-risk opioid analgesic use in the North Carolina Medicaid population.

3.5.3.1 Study Design—Aim 3

We used a retrospective cohort design to examine claims-based opioid exposure measures in the North Carolina Medicaid population that were most predictive of adverse clinical outcomes of high-risk opioid use (Figure 3.5). The purpose of this Aim was to inform optimal NC Medicaid lock-in program eligibility criteria. Aim 3 analyses used North Carolina Medicaid pharmacy and medical claims data and encompassed a study period of 10/1/2008 through 9/30/2010, representing the two years immediately preceding NC MLIP implementation. This study period allowed for investigation of optimal high-risk opioid use measures in the absence of any co-occurring effects of the NC MLIP policy on opioid utilization in the study cohort. A retrospective cohort was used consisting of adult NC Medicaid beneficiaries who received an opioid prescription during the first 10 months of the study period and did not have any administrative or clinical characteristics that would preclude them from being enrolled in the NC MLIP if MLIP eligibility criteria were met.

In order to identify and then validate optimal claims-based opioid exposure measures, we randomly assigned 50% of the study cohort to testing and validation samples.[243] This cross-validation method allowed evaluation of selected optimal opioid exposure measure performance in predicting primary and secondary outcomes in a sample of subjects entirely separate from those that contributed to the selection of these measures and measure thresholds.

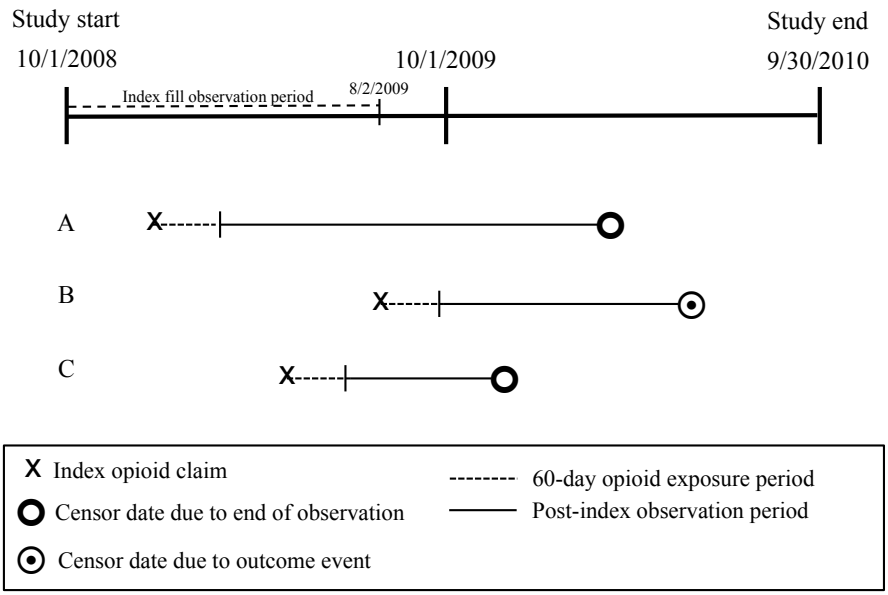
In the testing phase of Aim 3, we examined the performance of four opioid exposure measures in predicting Aim 3 outcomes. The opioid exposure measures included number of opioid prescription claims received, number of unique community and outpatient pharmacies used to obtain opioid prescriptions, average daily opioid dose (in mean MME/day), and average daily APAP dose from opioid/APAP combination products. Number of unique opioid prescribers was not measureable due to limitations in the study data provided to the researchers. All opioid exposure measures were assessed over a 60-day period beginning on the date of the index opioid prescription fill, which must have occurred between 10/1/08 through 8/2/09. A 60-day exposure assessment period was chosen to simulate current NC MLIP eligibility assessment practices. The primary clinical outcome of interest was an unintentional opioid overdose event, as defined in Section 3.4.1. This was considered the primary outcome, because accidental opioid overdose represented the most immediate and preventable outcome from high-risk opioid use behaviors. Secondary clinical outcomes included an unintentional APAP overdose event, an unintentional overdose event involving any drug product, an opioid use disorder diagnosis, and a substance use disorder diagnosis of any type. Subjects were observed for up to 365 days following the end of their 60-day exposure assessment period for the presence of an outcome event. A 365-day follow-up period was selected for generalizability to the 12-month MLIP enrollment period. For each opioid exposure/outcome pairing, the length of follow-up was determined either by the end of the study period, a lapse in NC Medicaid coverage, or the outcome event.

In the validation phase of Aim 3, we used the remaining 50% of subjects randomly assigned to the validation cohort to evaluate the performance of the best performing opioid exposure measures and thresholds from the testing phase. The same study design as the testing phase was used. Validation cohort

subjects' index opioid claim was identified between 10/1/08 through 8/2/09, at which point their opioid exposure was assessed for the following 60 days. However, opioid exposure assessment in the validation phase included dichotomous indicators for whether the subject met an opioid use criterion identified as optimal from testing phase analyses. Follow-up observation for an outcome event was also time dependent—as it was in the testing phase—and was right-censored either by the end of the 365-day maximum follow-up period, a lapse in NC Medicaid coverage, or the outcome event.

Figure 3.5 depicts the study design used in Aim 3 testing and validation phases. (This figure is dynamic with regard to each unique opioid exposure measure and clinical outcome pairing). Notable events include identification of the index opioid claim, 60-day opioid use assessment period, follow-up observation period after opioid use assessment, and end of subject observation. Subject A represents an individual who contributed the full 365 days of follow-up time without experiencing the given outcome. Subjects B and C contributed less than 365 days of follow-up due to experiencing the given outcome and having a lapse in continuous NC Medicaid coverage, respectively.

Figure 3.5: Aim 3 retrospective cohort study design for testing and validation phases



3.5.3.2 Study Cohort—Aim 3

The Aim 3 study cohort was selected from the initial population of all adults enrolled in NC Medicaid at any point during the study period of 10/1/08 through 9/30/10. The sample was then reduced to include all opioid users, defined as individuals who had a Medicaid prescription claim for an opioid analgesic between 10/1/08 through 8/2/09. Subjects were then excluded if they lacked 60 days of continuous NC Medicaid coverage following their index opioid fill date. For Aim 3, continuous NC Medicaid enrollment was defined as having no gaps in coverage greater than 15 days. In order to create a study cohort that closely mirrored the population of NC Medicaid beneficiaries that would be considered for MLIP enrollment if eligible, subjects were excluded who had dependent-living status (NC Medicaid living arrangement codes not equal to 10 or 11), dual Medicare coverage (Medicaid class codes B, E and Q), and a concomitant cancer diagnosis (ICD-9-CM 140-239 at any point during study observation). Subjects were excluded if they were less than 18 years of age or greater than 64 years of age at any point during their Aim 3 observation. Lastly, 50% random subsets of the final analytic cohort were created for distinct testing and validation samples (performed using STATA "cut" function for random uniform variable; seed=626; sorted on subject dummy ID).[243] Final Aim 3 cohort selection algorithm is presented below in Figure 4.8 in Section 4.3.1.

It should be noted that continuous NC Medicaid coverage following the 60-day opioid exposure assessment period was not applied as an inclusion criteria in testing and validation phases. Subjects were allowed to contribute varied follow-up observation time, up to a maximum of 365 days, for three primary reasons. First, including subjects with variable durations of continuous NC Medicaid coverage during follow-up allowed for enhanced sample size and capture of potentially rare overdose outcomes. Second, this allowed for use of time-to-event analyses, which only concerned the first instance of the outcome and were able to account for the timing of the outcome in relation to the opioid exposure assessment period. Third, requiring one year of continuous NC Medicaid coverage after the 60-day exposure period would have greatly reduced the generalizability of findings. Applying this requirement to the cohort would have resulted in a sample of subjects that, for each outcome event they experienced, would have had to have

received treatment for the event and survived (with NC Medicaid coverage) for the remainder of the 12-month follow-up period. Not requiring 365 days of continuous coverage allowed us to include subjects that received treatment for a study outcome during follow-up but died while receiving care or died at some point following discharge but prior to the end of the 365-day follow-up. (Study data limitations precluded capture of fatal overdose events that did not result in contact with the healthcare system).

3.5.3.3 Statistical Analyses—Aim 3

Univariate statistics were performed to describe the full sample, testing subset, and validation subset, while bivariate statistics were conducted to ensure successful random assignment of subjects to testing and validation samples with regard to key measures. Measures reported in these analyses included subject demographic characteristics of age, sex, and race; mean follow-up observation time; opioid exposure measure means; frequencies of outcome events; and mean time to outcome events. Chi-squared tests and independent sample t-tests were performed for bivariate analyses at an alpha level of 0.05. Analyses specific to the testing and validation phases are presented in distinct subsections below. Of note, all Aim 3 modeling that occurred in testing and validation phases were not adjusted for any covariates. This approach mirrored the real-world application of NC MLIP eligibility criteria for which patient-level characteristics outside of a given controlled substance use measure, such as age and sex, do not contribute to MLIP eligibility assessment.

3.5.3.3.1 Statistical Analyses—Aim 3 Testing Phase

In the testing phase of Aim 3, survival receiver operating characteristic (ROC) models were performed for each individual pairing of opioid exposure measure and outcome measure. Survival ROC employs a Kaplan-Meier time-to-event modeling approach to calculate time-dependent sensitivities and specificities of unique opioid exposure measure cutpoint values in discriminating between subjects that experienced and did not experience the outcome.[244-247] The survival ROC-produced sensitivities and (1-sensitivities) for each opioid exposure/outcome pairing were then plotted to determine the overall area under the curve (AUC), or c-index statistic. The AUC is a measure of discriminatory capability of the exposure measure in predicting the outcome. The AUC is bounded by 0.50 and 1.00 with 0.50 equaling

zero association between the exposure and outcome and 1.00 equaling perfect discrimination. AUC values were categorized as follows in terms of discriminatory capability: Excellent=0.90-1.00; good=0.80-0.89; fair=0.70-0.79; poor=0.60-0.69; and failure=0.50-0.59.[248] Optimal opioid exposure measure thresholds were derived from survival ROC modeling output using the measure of survival ROC plot Euclidean distance. Euclidean distance refers to the point on the survival ROC plot with the shortest distance to the (0,1) point on the figure, which represents 100% sensitivity and 100% specificity. Therefore the survival ROC-derived optimal threshold was defined as the value of the opioid exposure measure with the shortest Euclidean distance. This can also be characterized as the opioid exposure measure value with the highest joint sensitivity and specificity, calculated as: $1-\sqrt{[(1\text{-sensitivity})^2 + (1\text{-specificity})^2]}$. We reported survival ROC findings at a time point of 365 days, which results in a per-person-year interpretation of time-dependent AUCs, sensitivities, and specificities. This reflected analysis of key public health outcomes for the duration of a 12-month MLIP enrollment period.

Because the survival ROC statistical package in R (v3.1.3) did not allow for including multiple predictors in the survival ROC models, logistic regression ROC was performed to examine the discriminatory capability of combined opioid exposure measures. Logistic ROC models could not account for time dependent characteristics of the analytic dataset, so these models were performed in the full testing sample and among testing sample subjects who had a full year of continuous Medicaid coverage after their opioid exposure period.

After examining findings from the survival ROC models, it was determined that additional analysis was required to identify optimal thresholds of opioid exposure measures with alternative methods. Concerns existed over survival ROC-derived thresholds flagging more subjects as high-risk than would be feasible for MLIP enrollment based on real-world capacity of currently operating MLIPs. Therefore, time-to-event model log likelihood plots were used to identify the cutpoint(s) of an opioid exposure measure that maximized predictive fit with a given outcome.[249,250] For each exposure/outcome pairing, a series of bivariate Cox proportional hazard models predicting the time to Aim 3 outcome event

for each unique cutpoint of the exposure measure was performed. Each model produced a log likelihood value—a numerical representation of model fit—and the cutpoint value of the exposure measure maximizing the log likelihood was considered the optimal cutpoint for predicting that outcome.

Selection of optimal opioid exposure measures for further validation was informed by findings from survival ROC results. Selection of optimal opioid exposure measure thresholds was guided by results from the Cox model log likelihood plots. For both decisions, findings from models predicting the primary outcome of unintentional opioid overdose were weighed more heavily than those predicting secondary outcomes.

3.5.3.3.2 Statistical Analyses—Aim 3 Validation Phase

The performance of opioid exposure measures and their optimal thresholds selected in the testing phase was evaluated in the remaining 50% random sample of the Aim 3 cohort. For each opioid exposure criterion/outcome pair, we described frequencies of subjects meeting each criterion, frequencies of subjects experiencing outcomes, and the time-dependent sensitivities and specificities of each opioid exposure criterion at 365 days of follow-up. Bivariate Cox proportional hazard models estimating the effect of an opioid exposure criterion on an outcome was performed for each exposure/outcome pairing.[251] Hazard ratios and 95% confidence intervals were reported, as well as log likelihood values, which allowed comparison of exposure measure criterion performance in predicting a given outcome. Lastly, Kaplan-Meier survival function estimates were obtained to evaluate the performance of an opioid exposure measure threshold in predicting an outcome.[252] Kaplan-Meier survival functions were plotted for subjects at or above the opioid use measure threshold and subjects below the threshold. Using Kaplan-Meier estimates, absolute risk differences (ARD) for an outcome between those not flagged as high-risk by a criterion and those flagged as high-risk were reported for time periods of 30, 90, 180, and 365 days after opioid exposure assessment. Using the absolute risk differences at each time point, the number needed to enroll (NNE) figure was calculated as (1 / ARD). NNE was interpreted as the number of opioid users needed to enroll in an MLIP using a given opioid exposure criterion in order to have the opportunity to prevent one outcome event.

All validation phase analyses were performed for each individual opioid exposure criterion, the current NC MLIP criteria of ≥7 opioid fills, and all combinations of these opioid exposure criteria. Unconditional and conditional combinations of opioid exposure criteria were examined. For example, consider two unique opioid exposure measures: measure A and measure B. An unconditional combination required a subject to meet a threshold for high-risk opioid use for either measure A *or* measure B. This represented the current application of NC MLIP eligibility criteria, in which meeting at least one of three criteria qualifies someone for enrollment. Conditional combinations of opioid exposure criteria were also investigated, in which subjects were required to meet thresholds for both criterion A *and* criterion B.

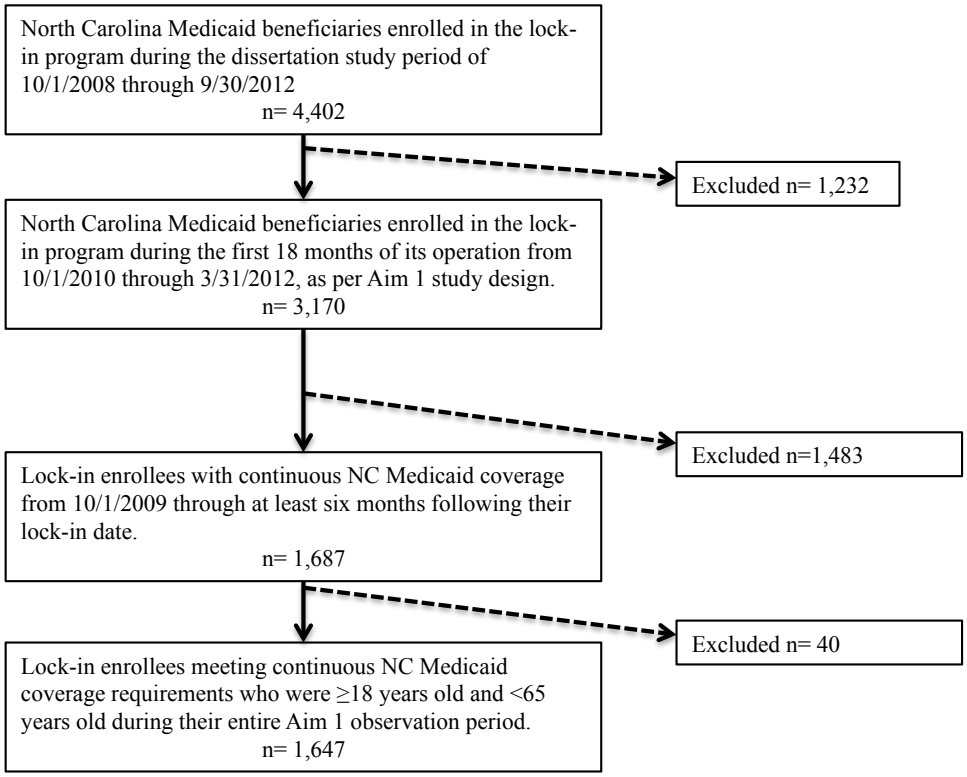
CHAPTER IV: RESULTS

4.1 AIM 1 RESULTS

4.1.1 Aim 1 Descriptive Analysis Findings

The Aim 1 analytic cohort included 1,647 study subjects. Figure 4.1 details the application of the inclusion criteria that led to subject selection. A total of 4,402 North Carolina Medicaid beneficiaries were enrolled in the Medicaid lock-in program during the study period. We excluded 1,232 subjects who were first enrolled in the MLIP after 3/31/12, which was beyond the first 18 months of program operation. An additional 1,483 subjects were excluded due to a lack of continuous enrollment in NC Medicaid beginning 10/1/2009 through at least six months following their MLIP enrollment. Lastly, 40 subjects were excluded who were less than 18 or greater than 65 years of age at any point during their observation.

Figure 4.1: Aim 1 analytic cohort selection



Prior to being locked in, 88%, 4%, and 69% of the Aim 1 cohort met the opioid use, benzodiazepine use, and pharmacy use criteria for MLIP enrollment, respectively (Table 4.1). Nearly two-thirds of subjects met exactly two MLIP eligibility criteria, while 31% satisfied a single criterion, and 1% met all three MLIP criteria prior to their lock-in. Roughly 5% of the sample was enrolled in the MLIP without previously meeting an MLIP eligibility criterion. This was possible due to an enrollment mechanism allowing providers to identify and recommend NC Medicaid beneficiaries for lock-in. The most common MLIP eligibility route in the sample (62%) was recording ≥7 opioid Medicaid claims in two calendar months, as well as using ≥4 opioid or benzodiazepine dispensing pharmacies in two calendar months.

Table 4.1: Aim 1 cohort MLIP eligibility, enrollment delay, and observation characteristics

MLIP characteristics	Total (n=1647)
Total subjects meeting MLIP criteria, n (%)	
Opioid use criterion met	1446 (87.8%)
Benzodiazepine use criterion met	58 (3.5%)
Pharmacy use measure met	1141 (69.3%)
Specific routes of MLIP eligibility, n(%)	
Single MLIP criterion met	511 (31.0%)
Opioid use only	411 (25.0%)
Benzodiazepine use only	14 (0.9%)
Pharmacies used only	86 (5.2%)
Two MLIP criteria met	1043 (63.3%)
Opioid use & benzodiazepine use	4 (0.2%)
Opioid use & pharmacy use	1015 (61.6%)
Benzodiazepine use & pharmacy use	24 (1.5%)
All three MLIP criteria met	16 (1.0%)
No MLIP criteria met	77 (4.7%)
Observation months, mean (SD)	
Total pre- and post-lock-in enrollment	31.4 (4.3)
Pre-lock-in enrollment	20.6 (5.0)
Post-lock-in enrollment	10.9 (1.8)
MLIP enrollment delay	
MLIP enrollment delayed, n (%)	1547 (93.9%)
Months enrollment delayed, mean (SD)	5.6 (3.9)

Note: MLIP= Medicaid lock-in program; SD=Standard deviation; Opioid eligibility = ≥7 opioid Medicaid claims in a two calendar month period; Benzodiazepine eligibility = ≥7 benzodiazepine Medicaid claims in a two calendar month period; Pharmacy use measure = opioid and/or benzodiazepine Medicaid claims from ≥4 unique pharmacies in a two calendar month period (proxy for the NC MLIP eligibility criterion of ≥4 unique prescribers).

On average, the total observation period for study subjects was 31 months, with 20 months coming prior to MLIP enrollment and 11 months of observation after enrollment in the MLIP (Table 4.2). Very few subjects were enrolled in the MLIP immediately after becoming eligible for lock-in. Specifically, 94% of subjects experienced a delay in MLIP enrollment of at least one calendar month. Enrollment delays were nearly six months, on average, and resulted from the phased-in implementation of the NC MLIP in which enrollment capacity increased monthly beginning in October 2010. This meant that nearly all subjects contributed data for the unique observation period in which they had demonstrated high-risk controlled substance use behaviors but had not yet experienced the MLIP policy intervention.

Figure 4.2 visualizes the temporal trends in total Aim 1 subjects eligible for and enrolled in the NC MLIP. This figure demonstrates how the phased-in MLIP implementation affected the rate of lock-in enrollment and contributed to enrollment delays. Roughly half of the 1,647 subjects included in Aim 1 first satisfied NC MLIP eligibility during the initial eligibility assessment period of August through October 2010. The total number of Aim 1 subjects eligible for the MLIP steadily increased across the study period. The high prevalence of MLIP enrollment delays is evident by the large gap between total MLIP enrollment numbers (red line) and total MLIP eligibility numbers (blue line). Only about 30 subjects were enrolled in the first month of operation in October 2010 despite roughly 800 being eligible. MLIP enrollment totals increased over the study period, reaching full capacity just two months prior to the end of the period of assessment for MLIP enrollment. The height of the cumulative MLIP enrollment line exceeded the height of the cumulative MLIP eligibility line in the final month due to the 70 subjects enrolled in the MLIP despite not meeting NC MLIP eligibility criteria in retrospective claims review.

Figure 4.2: Cumulative MLIP eligibility and enrollment totals for Aim 1 subjects across the study period

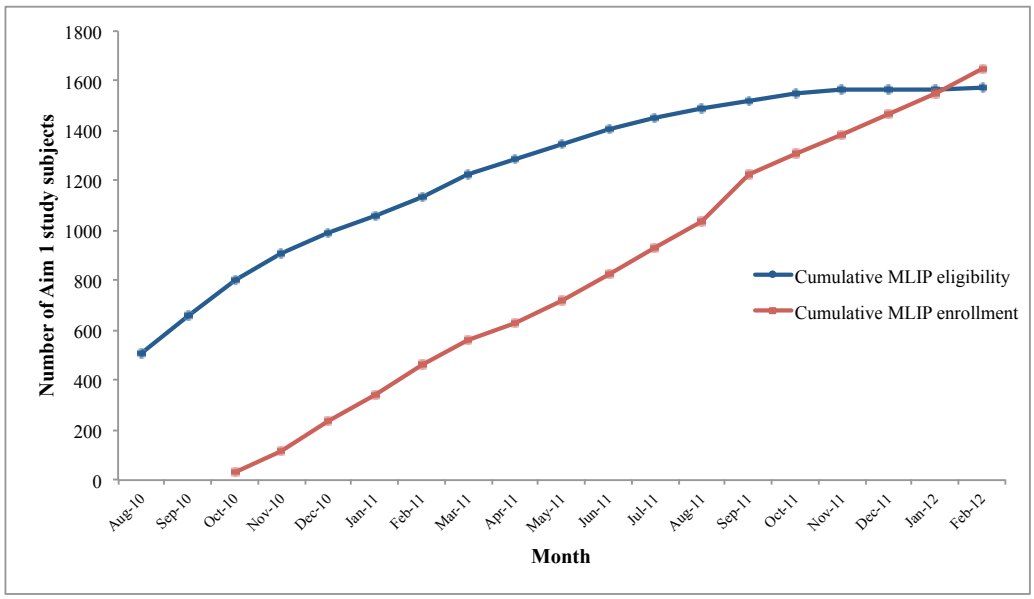


Table 4.2 presents summary statistics for the analytic cohort, including predisposing, enabling, and need variables for the entire sample and by route of MLIP eligibility. Overall, the study cohort had a mean age of 39.7 years and was predominantly female (73.5%) and White (75.8%). Predisposing characteristics were similar across sample subsets of MLIP enrollment eligibility based on opioid use, benzodiazepine use, and/or prescriber use. The 77 subjects that failed to meet any MLIP eligibility criteria prior to lock-in were more often White (81.8%) than the total sample and other eligibility criterion subsets.

The Aim 1 sample primarily resided in metropolitan areas, with 72.7% of subjects residing in a metropolitan county (RUCC score of 1-3). On average, a subject's county of residence at the time of MLIP enrollment had 50 community pharmacies and over 700 prescribers. However, pharmacy and prescriber supply varied widely across the sample. Over one-third of the sample reported living in a North Carolina county that bordered another state. County-level enabling characteristics were comparable across MLIP eligibility route subsets. The 58 people that were eligible due to high benzodiazepine use resided in metropolitan and border counties less often than subjects meeting any other eligibility criteria. Those who

were enrolled in the MLIP despite not meeting any eligibility criteria lived in metropolitan counties more often than subjects that met an eligibility criterion.

Need variable summary statistics indicated high prevalence of key comorbidities in the Aim 1 cohort. Nearly all subjects had a chronic noncancer pain diagnosis during the 12-month baseline period, and nearly 60% had an anxiety disorder. Forty-five to 55% of subjects recorded a diagnosis in the baseline period for a substance use disorder, depression, or any other mental health condition. The mean Charlson Comorbidity Index score was 1.4, which reflects a weighted aggregate score of the burden of physical comorbidities, excluding pain and mental health conditions. Subjects' physical comorbid burden were distributed relatively evenly when grouped into Charlson index scores of 0, 1, and ≥2. The Aim 1 cohort also received a high number of unique prescription drug products—controlled and non-controlled medications—during the 12-month baseline period, with a mean of 19.3 medications. Subjects eligible for the MLIP due to high benzodiazepine use had higher comorbidity burden compared to the total cohort.

Table 4.2: Summary statistics for predisposing, enabling, and need characteristics of the Aim 1 cohort, overall and by route of Medicaid lock-in program eligibility

Patient characteristic	Total (n=1647)	Opioid eligibility (n=1446)	Benzodiazepine eligibility (n=58)	Pharmacy eligibility (n=1141)	No eligibility (n=77)
Predisposing characteristics					
Age[1], mean (SD)	39.7 (10.5)	39.8 (10.6)	40.0 (10.7)	38.3 (10.4)	39.4 (10.3)
Female, n (%)	1211 (73.5%)	1069 (73.9%)	43 (74.1%)	823 (72.1%)	56 (72.7%)
Race, n (%)					
White	1248 (75.8%)	1076 (74.4%)	44 (75.9%)	859 (75.3%)	63 (81.8%)
Black	291 (17.7%)	268 (18.5%)	10 (17.2%)	206 (18.1%)	11 (14.3%)
Other/unknown	108 (6.6%)	102 (7.1%)	4 (6.9%)	76 (6.7%)	3 (3.9%)
Enabling characteristics[1,2]					
Metropolitan residency[3], n (%)	1197 (72.7%)	1060 (73.3%)	37 (63.8%)	831 (72.8%)	65 (84.4%)
Pharmacy supply, mean (SD)	49.3 (58.6)	50.3 (59.4)	42.0 (50.2)	52.3 (62.3)	37.9 (41.2)
Prescriber supply, mean (SD)	711.2 (942.7)	725.0 (950.4)	592.7 (815.8)	735.3 (975.4)	606.1 (834.7)
Border county, n (%)	600 (36.4%)	528 (36.5%)	10 (17.2%)	437 (38.4%)	24 (31.2)
Need characteristics[4]					
Charlson Comorbidity Index score, mean (SD)	1.4 (2.0)	1.4 (2.0)	1.6 (1.8)	1.2 (1.8)	1.2 (2.1)
Charlson score = 0, n (%)	676 (41.0%)	579 (40.0%)	20 (34.5%)	514 (45.1%)	38 (49.4%)
Charlson score = 1, n (%)	465 (28.2%)	411 (28.4%)	13 (22.4%)	322 (28.2%)	21 (27.3%)
Charlson score ≥ 2, n (%)	506 (30.7%)	456 (31.5%)	25 (43.1%)	305 (26.7%)	18 (23.4%)
Prescription drug burden, mean (SD)	19.3 (9.9)	19.5 (9.7)	17.0 (10.9)	17.7 (8.6)	18.8 (12.6)
Chronic non-cancer pain, n (%)	1583 (96.1%)	1396 (96.5%)	54 (93.1%)	1101 (96.5%)	68 (88.3%)
Anxiety disorder, n (%)	959 (58.2%)	817 (56.5%)	49 (84.5%)	660 (57.8%)	51 (66.2%)
Substance use disorder, n (%)	743 (45.1%)	614 (42.5%)	33 (56.9%)	516 (45.2%)	57 (74.0%)
Depression, n (%)	905 (55.0%)	774 (53.5%)	39 (67.2%)	592 (51.9%)	53 (68.8%)
Other mental illness, n (%)	836 (50.8%)	701 (48.5%)	40 (69.0%)	562 (49.3%)	50 (64.9%)

Note: Opioid eligibility = ≥7 opioid Medicaid claims in a two calendar month period; Benzodiazepine eligibility = ≥7 benzodiazepine Medicaid claims in a two calendar month period; Pharmacy eligibility = opioid and/or benzodiazepine Medicaid claims from ≥4 unique pharmacies in a two month period (proxy for unique prescriber measure used in practice); Study subjects could be included in multiple MLIP eligibility groups; SD=Standard deviation.

1. Age and county of residence measures reflect values of the measures at the time of a subject's enrollment in the lock-in program
2. All enabling characteristics were assessed at the county-level and reflect a subject's county of residence at time of lock-in enrollment.
3. Rural-urban continuum codes reflect 2013 version from the US Department of Agriculture, which ranges 1 to 9 with 1 being the most metropolitan counties and 9 being the most rural counties. Metropolitan counties have RUCC=1-3 and non-metropolitan counties=4-9
4. Clinical characteristics were assessed for all subjects during the 12-month baseline period from 10/1/2009 to 9/30/2010

4.1.2 Aim 1 Bivariate Analysis Findings

The longitudinal Aim 1 cohort obtained an average of 2.56 combined opioid and benzodiazepine prescription fills per-person-per-month across the entire study period. This figure includes Medicaid-covered fills and circumvented fills (Table 4.3). Three-fourths of these fills were for opioid analgesics. When comparing before and after MLIP enrollment in bivariate analysis, total overall fills of these medications from any payment source decreased 17% (p<0.001).

Table 4.3: Bivariate trends in opioid and benzodiazepine prescription fills and prescribers, before and after enrollment in the lock-in program

	Total (n=1647)		Before MLIP enrollment (n=1647)		After MLIP enrollment (n=1647)		Percent change	P-value
Monthly total prescription fills per person (Medicaid + circumvented), mean (SD)								
Opioid + benzodiazepine	2.56	(2.06)	2.72	(2.13)	2.26	(1.89)	-17%	<0.001
Opioid	1.90	(1.79)	2.04	(1.87)	1.62	(1.58)	-21%	<0.001
Benzodiazepine	0.67	(0.84)	0.68	(0.85)	0.65	(0.82)	-5%	<0.001
Monthly Medicaid claims per person, mean (SD)								
Opioid + benzodiazepine	2.07	(1.86)	2.43	(1.94)	1.39	(1.50)	-43%	<0.001
Opioid	1.52	(1.59)	1.82	(1.70)	0.95	(1.19)	-48%	<0.001
Benzodiazepine	0.55	(0.74)	0.61	(0.77)	0.44	(0.66)	-28%	<0.001
Monthly unique opioid and benzodiazepine Medicaid prescribers per person, mean (SD)	0.99	(0.81)	1.18	(0.87)	0.64	(0.52)	-46%	<0.001
Number of subjects with any circumvented prescriptions, n (%)								
Opioid + benzodiazepine	1566	(95%)	1337	(81%)	1436	(87%)	7%	<0.001
Opioid	1527	(93%)	1254	(76%)	1354	(82%)	8%	<0.001
Benzodiazepine	989	(60%)	577	(35%)	800	(49%)	39%	<0.001
Percent of person-months with any circumvented prescriptions, (%)								
Opioid + benzodiazepine	26.1%		17.6%		42.3%		140%	<0.001
Opioid	21.5%		14.5%		34.9%		141%	<0.001
Benzodiazepine	8.8%		5.2%		15.6%		200%	<0.001
Total monthly circumvented prescriptions per person, mean (SD)								
Opioid + benzodiazepine	0.50	(1.13)	0.30	(0.85)	0.87	(1.45)	195%	<0.001
Opioid	0.38	(0.96)	0.23	(0.72)	0.67	(1.24)	193%	<0.001
Benzodiazepine	0.11	(0.42)	0.07	(0.32)	0.20	(0.55)	204%	<0.001

Note: MLIP=Medicaid lock-in program; SD=Standard deviation. The pre-MLIP enrollment period consisted of 33,882 person-months, while the post-MLIP enrollment period consisted of 17,916 person-months

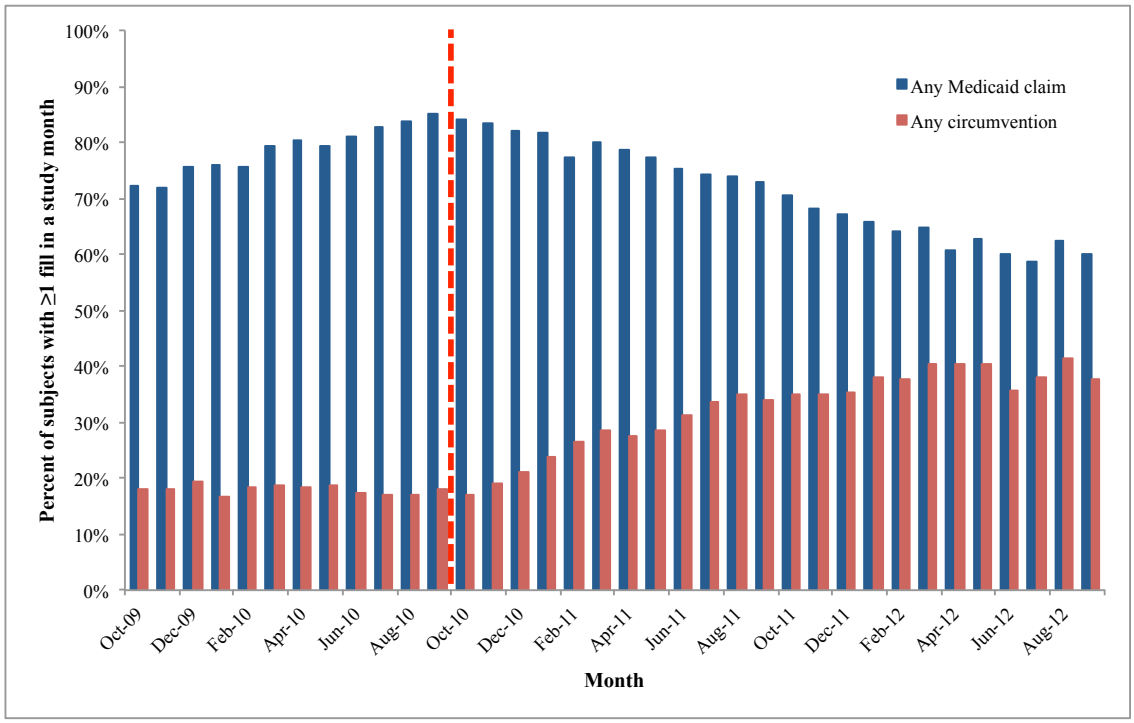
When looking only at Medicaid-covered opioid and benzodiazepine fills—which reflects the perspective of NC MLIP administrators who were not able to observe circumvention—the average monthly Medicaid claims for these drugs decreased 43% from 2.43 to 1.39 fills per-person-per-month after MLIP enrollment ($p<0.001$). Most of this reduction in Medicaid controlled substance claims was attributable to fewer opioid Medicaid claims. A similar trend was observed in the mean number of unique opioid and benzodiazepine prescribers of Medicaid-paid fills. Aim 1 subjects used an average of 1.18 unique Medicaid prescribers per-person-per-month before MLIP enrollment compared to 0.64 unique prescribers prior to being locked in ($p<0.001$). These findings indicate that, from an NC Medicaid administrator's perspective, the MLIP appeared to result in an over 40% decrease in the utilization of opioids, benzodiazepines, and controlled substance prescribers in bivariate analysis.

However, circumvention of opioids and benzodiazepines was highly prevalent in the Aim 1 cohort. It also increased significantly after enrollment in the NC MLIP in bivariate analysis. Roughly 95% of subjects circumvented their Medicaid coverage to obtain an opioid or benzodiazepine prescription fill at any point in the entire study period. The proportion of subjects engaging in any circumvention increased slightly from 81% in the pre-MLIP enrollment observation period to 87% in the post-MLIP enrollment period ($p<0.001$). The proportion of person-months in which a circumvented opioid or benzodiazepine fill occurred was nearly 2.5 times higher in the post-MLIP enrollment period compared to the pre-MLIP enrollment period (42.3% vs. 17.6%, $p<0.001$). In all, the mean number of circumvented opioid and benzodiazepine fills per-person-per-month nearly tripled from 0.30 to 0.87 circumvented fills before and after MLIP enrollment, respectively ($p<0.001$).

Figures 4.3 and 4.4 visualize trends in circumvented and Medicaid-paid controlled substance prescription fills for the Aim 1 cohort across the entire study period. There was a gradual increase in the proportion of subjects engaging in circumvention after implementation of the NC MLIP in October 2010 (Figure 4.3). In each of the 12 months leading up to the start of the NC MLIP, roughly 17% of subjects received as least one opioid or benzodiazepine prescription through circumvention. After the NC MLIP was introduced, the proportion of subjects engaging in circumvention rose steadily to 40% 24 months into

program operation. This was coupled by a corresponding decrease in the proportion of subjects obtaining an opioid or benzodiazepine prescription through the NC Medicaid benefit during the same time period.

Figure 4.3: Trends in the proportion of Aim 1 subjects recording any opioid or benzodiazepine fill in an observation month, by source of payment

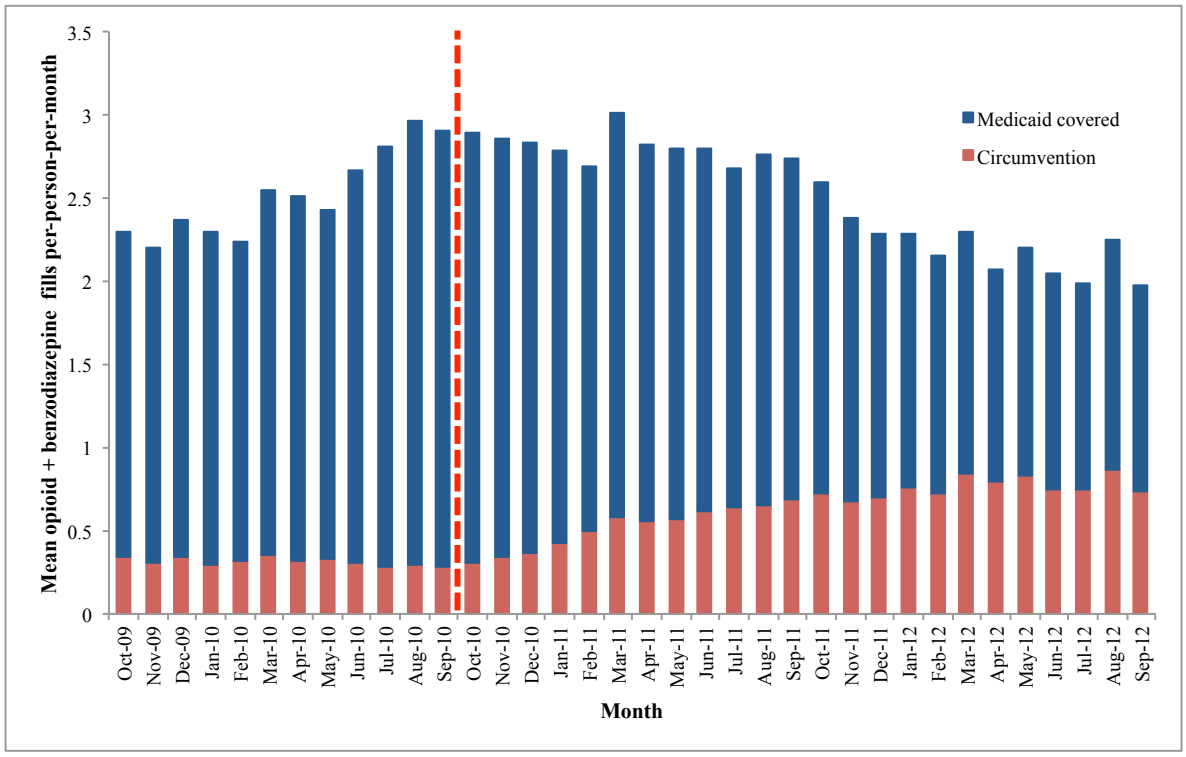


Note: Red dotted line delineates North Carolina Medicaid lock-in program implementation

Figure 4.4 depicts the mean opioid plus benzodiazepine prescription fill totals per person per month across the Aim 1 study period. The height of the column represents the mean total opioid and benzodiazepine fills obtained by a subject regardless of payment source. Each column is divided into the proportion of mean total controlled substance fills attributable to circumvention and use of the Medicaid benefit. Circumvention was stable prior to MLIP implementation in October 2010 at around 0.3 circumvented fills per-person-per-month. After October 2010, circumvention events increased steadily to around 0.8 circumvented fills per-person-per-month after 24 months of NC MLIP operation. Subjects filled an average of 2.6 Medicaid-covered opioid and benzodiazepines prescriptions at the start of the NC

MLIP. There was a corresponding decrease in Medicaid controlled substance fills to 1.6 fills per person per month over the 24 months of NC MLIP operation observed in the study. Total receipt of these medications—through Medicaid and circumvention—also experienced a decline from October 2010 through September 2012.

Figure 4.4: Trends in mean opioid plus benzodiazepine prescription fill totals per-person-per-month for the Aim 1 cohort, by payment source



Note: Red dotted line delineates North Carolina Medicaid lock-in program implementation

4.1.3 Aim 1 Generalized Estimating Equation Analysis Findings

Table 4.4 presents findings from primary analyses in which generalized estimating equations modeled the effect of MLIP enrollment and patient-level predictors on the likelihood of receiving a circumvented opioid or benzodiazepine fill and the rate of circumvention. The left columns present risk ratio estimates for the likelihood of receiving a circumvented opioid or benzodiazepine prescription fill in a person-month. The right columns present incidence rate ratio estimates for the rate of circumvented prescription fills in a person-month.

MLIP enrollment was associated with 3.6 times higher likelihood of controlled substance circumvention (RR=3.55; 95% CI: 3.13, 4.03) compared to months in which subjects were not enrolled in the MLIP, controlling for time, the overall policy period, and patient-level covariates. The probability of circumvention was 28% higher when subjects were in a period of delayed enrollment after first meeting eligibility for the lock-in program (RR=1.28; 95% CI: 1.13, 1.46). As time spent in an MLIP enrollment delay increased, the probability of circumvention increased slightly, but significantly (RR=1.02; 95% CI; 1.00, 1.03). MLIP eligibility stemming from high utilization of benzodiazepines and controlled substance providers (using the proxy measure of unique dispensing pharmacies) was associated with a 52% (RR=1.52, 95% CI: 1.29, 1.79) and 10% (RR=1.16; 95% CI: 1.01, 1.21) higher likelihood of engaging in circumvention, respectively. It is worth noting the binary indicator for the overall MLIP policy period had a significantly negative relationship with the likelihood of circumvention. However, this finding has limited interpretability when controlling for variation in the outcome due to the key independent variable of MLIP enrollment. The MLIP policy indicator was included in the final models to control for any ambient effect of the MLIP's existence on patient behavior whether or not they were enrolled in the MLIP.

Table 4.4: Generalized estimating equation results for the estimation of any circumvention fill and number of circumvented fills

	Any circumvented fill			Number of circumvented fills		
Variable	RR	(95% CI)	P-value	IRR	(95% CI)	P-value
Key independent variable						
MLIP enrollment (Key IV)	3.55	(3.13, 4.03)	<0.001	4.40	(3.76, 5.15)	<0.001
MLIP policy variables						
MLIP enrollment * month	1.00	(0.99, 1.01)	0.675	1.01	(0.99, 1.02)	0.274
MLIP enrollment delay	1.28	(1.13, 1.46)	<0.001	1.25	(1.06, 1.47)	0.008
MLIP enrollment delay * month	1.02	(1.00, 1.03)	0.031	1.02	(1.00, 1.05)	0.036
Month	1.00	(0.99, 1.01)	0.766	0.98	(0.97, 1.00)	0.025
MLIP policy period	0.81	(0.73, 0.91)	<0.001	0.88	(0.77, 1.01)	0.074
MLIP policy period * month	0.99	(0.98, 1.00)	0.099	1.00	(0.98, 1.01)	0.645
MLIP eligibility route						
Opioid use	1.01	(0.87, 1.16)	0.928	1.10	(0.92, 1.31)	0.283
Benzodiazepine use	1.52	(1.29, 1.79)	<0.001	1.78	(1.47, 2.16)	<0.001
Pharmacy use	1.10	(1.01, 1.21)	0.028	1.18	(1.03, 1.35)	0.018
No eligibility criteria met	0.94	(0.72, 1.22)	0.628	0.96	(0.68, 1.36)	0.834
Predisposing characteristics						
Age	0.994	(0.99, 1.00)	0.001	0.99	(0.99, 1.00)	0.017
Female	0.94	(0.86, 1.02)	0.144	0.88	(0.78, 1.00)	0.053
Race (White referent)						
Black	0.99	(0.90, 1.10)	0.892	0.97	(0.83, 1.13)	0.658
Other	0.96	(0.82, 1.11)	0.551	0.91	(0.74, 1.12)	0.368
Enabling characteristics						
Metropolitan residence	1.01	(0.93, 1.10)	0.806	1.03	(0.91, 1.17)	0.602
County pharmacy supply (<10 referent)						
11-25	1.05	(0.95, 1.17)	0.343	1.03	(0.89, 1.19)	0.673
26-50	1.10	(0.99, 1.22)	0.071	1.06	(0.92, 1.23)	0.414
51-100	1.07	(0.96, 1.20)	0.220	1.04	(0.89, 1.22)	0.623
>100	1.22	(1.07, 1.39)	0.004	1.33	(1.08, 1.65)	0.008
Border county	1.00	(0.93, 1.07)	0.925	1.01	(0.90, 1.14)	0.817
Need characteristics						
Chronic non-cancer pain	1.33	(1.06, 1.68)	0.013	1.48	(1.11, 1.96)	0.008
Anxiety disorder	1.12	(1.04, 1.22)	0.003	1.11	(0.98, 1.25)	0.100
Substance abuse disorder	1.01	(0.94, 1.08)	0.874	1.03	(0.93, 1.15)	0.573
Depression	1.07	(0.99, 1.16)	0.071	1.11	(0.99, 1.24)	0.070
Other mental illness	1.05	(0.98, 1.13)	0.195	1.03	(0.93, 1.15)	0.542
Charlson Comorbidity Index score						
0 (referent)						
1	1.00	(0.92, 1.09)	0.979	0.98	(0.87, 1.11)	0.753
≥2	1.14	(1.03, 1.25)	0.010	1.15	(0.99, 1.34)	0.074
Prescription drug burden	1.00	(0.99, 1.00)	0.473	1.00	(0.99, 1.01)	0.417

Note: RR=relative risk; CI=confidence interval; IRR=incidence rate ratio; MLIP=Medicaid lock-in program. RR were obtained through generalized estimating equation (GEE) modeling with monthly measures using Poisson distribution, log link, and autoregressive (1 month) correlation structure with robust standard errors. IRR were obtained through GEE using Poisson distribution, log link, and autoregressive correlation structure with robust standard errors.

Patient age was the only statistically significant predisposing predictor of engaging in any circumvention. Each increase in age of one year was associated with a small, but significant, reduction in the likelihood of circumvention (RR=0.994; 95% CI: 0.99, 1.00). Sex and race were not predictive of

circumvention in this MLIP enrollee cohort. With regard to patient predisposing characteristics, living in a metropolitan county or a border county were not associated with circumvention. However, patients that resided in counties with a supply of more than 100 community pharmacies had a 22% higher likelihood of circumvention compared to those that lived in counties with 10 or fewer pharmacies (RR=1.22; 95% CI: 1.07, 1.39). Receipt of a prior diagnosis of chronic noncancer pain (RR=1.33; 95% CI: 1.06, 1.68) or an anxiety disorder (RR=1.12; 95% CI: 1.04, 1.22) was associated with significantly higher probability of receiving a circumvented fill compared to subjects without these conditions. Subjects with a depression diagnosis had 7% higher likelihood of circumvention, but this finding fell slightly short of statistical significance based on an alpha level of ≤0.05. Patients with the highest burden of physical comorbidities, defined as a Charlson score of 2 or more, were significantly more likely to circumvent compared to those with a Charlson score of 0 (RR=1.14; 95% CI: 1.03, 1.25).

Similar findings were reported in the GEE model that used a Poisson count model approach to estimate the number, or extent, of circumvention events (as seen in the right column set in Table 4.4 denoted as incidence rate ratios). The rate of circumvention events was 4.4 times higher when subjects were enrolled in the MLIP (IRR=4.40; 95% CI: 3.76, 5.15), compared to when they were not enrolled in the MLIP, controlling for policy and patient-level covariates. Periods of delayed MLIP enrollment were also associated with a significantly higher rate of circumvention events (IRR=1.25; 95% CI: 1.06, 1.47). When looking at patient-level characteristics, patient age, living in a county with >100 community pharmacies, and having a baseline diagnosis of chronic noncancer pain were significant predictors of higher numbers of circumvention events. Female sex had a strong, but not statistically significant, association with reduced rate of circumvention (IRR=0.88; 95% CI: 0.78, 1.00). Anxiety diagnosis, depression diagnosis, and a Charlson score of 2 or more were all strongly positive, but not statistically significant, predictors of the extent of circumvention in a given month.

4.2 AIM 2 RESULTS

4.2.1 Aim 2 Descriptive and Bivariate Analysis Findings

The Aim 2 analytic cohort included 1,646 NC MLIP enrollees with opioid use during the study period of 10/1/2009 through 9/30/2012. This was the same study cohort used in Aim 1 analyses. However, one additional subject was excluded due to having only benzodiazepine use. The selection algorithm was presented previously in Figure 4.1. Aim 2 subjects were enrolled in the NC MLIP between 10/1/2010 and 3/31/2012, had continuous NC Medicaid coverage from 10/1/2009 through at least six months following their MLIP enrollment date, and were ages 18-64.

Patient-level predisposing, enabling, need, and MLIP enrollment characteristics of the study cohort were described previously in Aim 1, Section 4.1.1. Therefore, we focus on reporting descriptive and bivariate analysis findings of prescription-level opioid use characteristics of the cohort. The three Aim 2 prescription-level outcomes of Schedule II opioid use, long-acting opioid use, and average daily prescribed opioid dose in mean MME/day are emphasized.

Tables 4.5a-c report frequencies of total opioid prescription fills, Schedule II opioid fills, long-acting opioid fills, and mean prescribed MME/day. Bivariate comparisons of these measures across MLIP enrollment status are also reported. These data presented are grouped by payment source—circumvented, Medicaid paid, and all payers—for comprehension but will be detailed here in aggregate.

The Aim 2 cohort received a total of 98,243 opioid prescriptions during the study period. Of these, 19,778 were obtained through circumvention, while the remaining 78,465 opioid prescriptions were paid for using the Medicaid benefit.

Table 4.5a: Circumvented opioid prescription frequencies in the Aim 2 cohort by prescription-level characteristic and MLIP enrollment status

	Total (n=19,778)	Pre-MLIP enrollment (n=7,781)	Post-MLIP enrollment (n=11,997)	% Change	p-value
Schedule II (vs. Schedule III-V) opioid fills, n (%)	10869 (55.0%)	4314 (55.4%)	6555 (54.6%)	-1%	0.270
Long-acting (vs. short-acting) opioid fills, n (%)	2097 (10.6%)	968 (12.4%)	1129 (9.4%)	-24%	<0.001
Prescribed MME/day per opioid Rx, mean (SD)	63.8 (86)	68.4 (101)	60.8 (75)	-11%	<0.001

Table 4.5b: Medicaid paid opioid prescription frequencies in the Aim 2 cohort by prescription-level characteristic and MLIP enrollment status

	Total (n=78,465)	Pre-MLIP enrollment (n=61,517)	Post-MLIP enrollment (n=16,948)	% Change	p-value
Schedule II (vs. Schedule III-V) opioid fills, n (%)	48551 (61.9%)	35726 (58.1%)	12825 (75.7%)	30%	<0.001
Long-acting (vs. short-acting) opioid fills, n (%)	15271 (19.5%)	9888 (16.1%)	5383 (31.8%)	98%	<0.001
Prescribed MME/day per opioid Rx, mean (SD)	83.4 (140)	75.7 (120)	111 (194)	47%	<0.001

Table 4.5c: All-payer opioid prescription frequencies in the Aim 2 cohort by prescription-level characteristic and MLIP enrollment status

	Total (n=98,243)	Pre-MLIP enrollment (n=69,298)	Post-MLIP enrollment (n=28,945)	% Change	p-value
Schedule II (vs. Schedule III-V) opioid fills, n (%)	59420 (60.5%)	40040 (57.8%)	19380 (67.0%)	16%	<0.001
Long-acting (vs. short-acting) opioid fills, n (%)	17368 (17.7%)	10856 (15.7%)	6512 (22.5%)	43%	<0.001
Prescribed MME/day per opioid Rx, mean (SD)	79.4 (131)	74.8 (118)	90.5 (158)	21%	<0.001

Note: MLIP=Medicaid lock-in program; MME=Milligram morphine equivalent; Rx=Prescription; SD=Standard deviation

Sixty-two percent of all opioid prescriptions paid for with the Medicaid benefit were written for Schedule II products, while 55.0% of all circumvented opioid prescriptions contained Schedule II opioids. There was no change in the proportion of circumvented opioid prescriptions written for Schedule II opioids after subjects were enrolled in the NC MLIP (p=0.270). However, a significantly larger

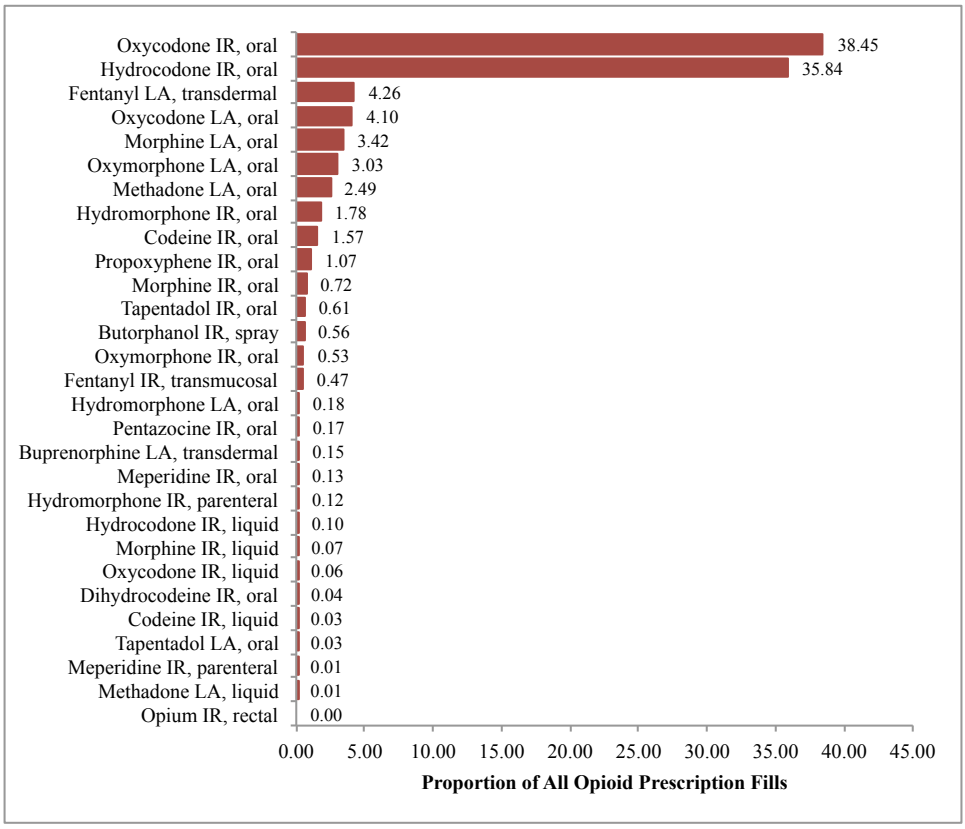
proportion of Medicaid covered opioid prescriptions contained Schedule II products after MLIP enrollment (58.1% pre-MLIP enrollment vs. 75.7% post-MLIP enrollment; $p<0.001$).

Long-acting opioid prescription fills were less prevalent than Schedule II opioid fills, with 19.5% of all Medicaid covered opioid prescriptions and 10.6% of all circumvented opioid fills written for long-acting opioid products. After NC MLIP enrollment, the proportion of circumvented opioid fills written for long-acting opioid formulations experienced a relative decrease of 24% (12.4% pre-MLIP enrollment vs. 9.4% post-MLIP enrollment; $p<0.001$). However, the proportion of opioid prescriptions obtained by subjects through NC Medicaid nearly doubled after MLIP enrollment (16.1% pre-MLIP enrollment vs. 31.8% post-MLIP enrollment; $p<0.001$).

Similar trends were observed for the average prescribed MME/day per prescription for the Aim 2 cohort. On average, opioid prescriptions obtained through the NC Medicaid benefit had a mean MME/day of 83.4 for the entire study period. Circumvented opioid prescriptions had a lower mean daily opioid dose of 63.8 MME/day. The mean MME/day of opioid prescriptions that subjects obtained through circumvention decreased significantly from 68.4 to 60.8 MME/day ($p<0.001$) after enrollment in the NC MLIP. However, opioid fills obtained through the NC Medicaid benefit experienced a nearly 50% increase in average daily opioid dose per prescription after subjects were enrolled in the MLIP (75.7 MME/day pre-MLIP enrollment vs. 111.0 MME/day post-MLIP enrollment; $p<0.001$).

Figure 4.5 depicts of the frequency of opioid products obtained by the study cohort across the entire study period. Three-fourths of all opioid prescriptions contained short acting oxycodone tablets/capsules or short acting hydrocodone tablets/capsules. The next five most commonly prescribed opioid products were all long acting opioid preparations, making up 2.5% to 4.3% of total opioid use individually. These included fentanyl transdermal patches, long acting oxycodone tablets, long acting morphine tablets/capsules, long acting oxymorphone tablets, and methadone tablets/capsules. The remaining 8.4% of all opioid prescription fills received by study subjects were comprised of 22 different opioid products.

Figure 4.5: Ranked frequency of opioid products obtained by the Aim 2 cohort



Note: IR=Immediate release; LA=Long acting

The next series of tables (4.6a-b; 4.7a-b; 4.8a-b; and 4.9a-b) describes the ranked frequency of the most commonly received Schedule II, Schedule III-V, long acting, and short acting opioid products broken down by payment source and MLIP enrollment status. Short acting oxycodone tablets/capsules was by far the most commonly circumvented Schedule II opioid product before (69.5%) and after (75.2%) subjects were enrolled in the MLIP (Table 4.6a). Long acting oxycodone tablets and fentanyl transdermal patches were less commonly circumvented after MLIP enrollment. Among non-Schedule II products obtained through circumvention, prescriptions for short acting hydrocodone tablets comprised over 90% of all circumvented Schedule III-V opioids (Table 4.6b).

Table 4.6a: Circumvented Schedule II opioid product frequency, by MLIP enrollment status

Pre-MLIP enrollment				Post-MLIP enrollment			
Rank	**Freq.**	**%**	**Product**	**Rank**	**Freq.**	**%**	**Product**
1	2,996	69.5	Oxycodone IR, oral	1	4,931	75.2	Oxycodone IR, oral
2	328	7.6	Oxycodone LA, oral	3	327	5.0	Methadone LA, oral
3	293	6.8	Methadone LA, oral	6	241	3.7	Morphine LA, oral
4	165	3.8	Hydromorphone IR, oral	4	227	3.5	Hydromorphone IR, oral
5	161	3.7	Fentanyl LA, transdermal	2	201	3.1	Oxycodone LA, oral

Table 4.6b: Circumvented Schedule III-V opioid product frequency, by MLIP enrollment status

Pre-MLIP enrollment				Post-MLIP enrollment			
Rank	**Freq.**	**%**	**Product**	**Rank**	**Freq.**	**%**	**Product**
1	3,122	90.1	Hydrocodone IR, oral	1	5,022	92.3	Hydrocodone IR, oral
2	150	4.3	Propoxyphene IR, oral	3	325	6.0	Codeine IR, oral
3	103	3.0	Codeine IR, oral	5	37	0.7	Butorphanol IR, spray
4	58	1.7	Pentazocine IR, oral	6	27	0.5	Hydrocodone IR, liquid
5	15	0.4	Butorphanol IR, spray	7	11	0.2	Buprenorphine LA, transdermal

Note: MLIP=Medicaid lock-in program; Freq=Frequency; IR=Immediate release; LA=Long acting. Post-MLIP enrollment period ranks reflect that specific product's frequency rank in the pre-MLIP enrollment period.

Schedule II opioid products paid for with the Medicaid benefit prior to MLIP enrollment had a similar profile to circumvented Schedule II opioid prescriptions in this period (Table 4.7a). Short acting oxycodone tablets/capsules made up about two-thirds of these prescriptions, with long acting oxycodone tablets comprising over 7%. After MLIP enrollment, short acting oxycodone tablets/capsules were still the most common Schedule II opioid obtained through Medicaid but it represented a smaller share (51.0%). Long acting oxymorphone, oxycodone, and morphine products comprised a larger proportion of Medicaid paid opioid fills after MLIP enrollment. Short acting hydrocodone tablets again represented the vast majority of Medicaid paid Schedule III-V opioid fills obtained by subjects before and after MLIP enrollment (Table 4.7b).

Table 4.7a: Medicaid paid Schedule II opioid product frequency, by MLIP enrollment status

Pre-MLIP enrollment				Post-MLIP enrollment			
Rank	**Freq.**	**%**	**Product**	**Rank**	**Freq.**	**%**	**Product**
1	23,312	65.3	Oxycodone IR, oral	1	6,540	51.0	Oxycodone IR, oral
2	2,543	7.1	Oxycodone LA, oral	5	1,388	10.8	Oxymorphone LA, oral
3	2,452	6.9	Fentanyl LA, transdermal	3	1,379	10.8	Fentanyl LA, transdermal
4	2,069	5.8	Morphine LA, oral	2	957	7.5	Oxycodone LA, oral
5	1,387	3.9	Oxymorphone LA, oral	4	931	7.3	Morphine LA, oral

Table 4.7b: Medicaid paid Schedule III-V opioid product frequency, by MLIP enrollment status

Pre-MLIP enrollment				Post-MLIP enrollment			
Rank	**Freq.**	**%**	**Product**	**Rank**	**Freq.**	**%**	**Product**
1	23,293	90.3	Hydrocodone IR, oral	1	3,775	91.6	Hydrocodone IR, oral
2	984	3.8	Codeine IR, oral	4	119	2.9	Butorphanol IR, spray
3	900	3.5	Propoxyphene IR, oral	2	118	2.9	Codeine IR, oral
4	375	1.5	Butorphanol IR, spray	7	91	2.2	Buprenorphine LA, transdermal
5	96	0.4	Pentazocine IR, oral	5	6	0.2	Pentazocine IR, oral

Note: MLIP=Medicaid lock-in program; Freq=Frequency; IR=Immediate release; LA=Long acting. Post-MLIP enrollment period ranks reflect that specific product's frequency rank in the pre-MLIP enrollment period.

Table 4.8a and 4.8b describe the frequency of long acting and short acting opioid products, respectively, obtained by subjects through circumvention. Long acting oxycodone and methadone products comprised nearly two-thirds of all circumvented long acting opioid prescriptions prior to MLIP enrollment (Table 4.8a). Fentanyl transdermal patches and long acting morphine tablets/capsules contributed another 30% of pre-MLIP enrollment circumvention behavior. After MLIP enrollment, though, the prevalence of circumvented long acting oxycodone was reduced by half, and the prevalence of circumvented long acting morphine prescriptions increased from 12.6% to 21.4%. Short acting hydrocodone and oxycodone tablets/capsules comprised roughly 90% of all short acting opioid products obtained through circumvention before and after MLIP enrollment (Table 4.8b).

Table 4.8a: Circumvented long acting opioid product frequency, by MLIP enrollment status

Pre-MLIP enrollment				Post-MLIP enrollment			
Rank	**Freq.**	**%**	**Product**	**Rank**	**Freq.**	**%**	**Product**
1	328	33.9	Oxycodone LA, oral	2	327	29.0	Methadone LA, oral
2	293	30.3	Methadone LA, oral	4	241	21.4	Morphine LA, oral
3	161	16.6	Fentanyl LA, transdermal	1	201	17.8	Oxycodone LA, oral
4	122	12.6	Morphine LA, oral	3	196	17.4	Fentanyl LA, transdermal
5	56	5.8	Oxymorphone LA, oral	5	149	13.2	Oxymorphone LA, oral

Table 4.8b: Circumvented short acting opioid product frequency, by MLIP enrollment status

Pre-MLIP enrollment				Post-MLIP enrollment			
Rank	**Freq.**	**%**	**Product**	**Rank**	**Freq.**	**%**	**Product**
1	3,122	45.8	Hydrocodone IR, oral	1	5,022	46.2	Hydrocodone IR, oral
2	2,996	44.0	Oxycodone IR, oral	2	4,931	45.4	Oxycodone IR, oral
3	165	2.4	Hydromorphone IR, oral	5	325	3.0	Codeine IR, oral
4	150	2.2	Propoxyphene IR, oral	3	227	2.1	Hydromorphone IR, oral
5	103	1.5	Codeine IR, oral	9	92	0.9	Morphine IR, oral

Note: MLIP=Medicaid lock-in program; Freq=Frequency; IR=Immediate release; LA=Long acting. Post-MLIP enrollment period ranks reflect that specific product's frequency rank in the pre-MLIP enrollment period.

Long acting oxycodone tablets/capsules and fentanyl transdermal patches each represented a quarter of all Medicaid paid long acting opioid prescriptions before MLIP enrollment (Table 4.9a). After MLIP enrollment, long acting oxymorphone products replaced long acting oxycodone as the most common long acting opioid product obtained through Medicaid. Although methadone prescriptions were among the most commonly circumvented long acting product, methadone products were only the fifth-most common prescriptions among Medicaid paid Schedule II opioid fills. Similarly to previous findings, short acting oxycodone and hydrocodone prescriptions represented the vast majority of short acting opioid prescriptions obtained through the Medicaid benefit (Table 4.9b).

Table 4.9a: Medicaid paid long acting opioid product frequency, by MLIP enrollment status

Pre-MLIP enrollment				**Post-MLIP enrollment**			
Rank	**Freq.**	**%**	**Product**	**Rank**	**Freq.**	**%**	**Product**
1	2,543	25.7	Oxycodone LA, oral	4	1,388	25.8	Oxymorphone LA, oral
2	2,452	24.8	Fentanyl LA, transdermal	2	1,379	25.6	Fentanyl LA, transdermal
3	2,069	20.9	Morphine LA, oral	1	957	17.8	Oxycodone LA, oral
4	1,387	14.0	Oxymorphone LA, oral	3	931	17.3	Morphine LA, oral
5	1,290	13.1	Methadone LA, oral	5	532	9.9	Methadone LA, oral

Table 4.9b: Medicaid paid short acting opioid product frequency, by MLIP enrollment status

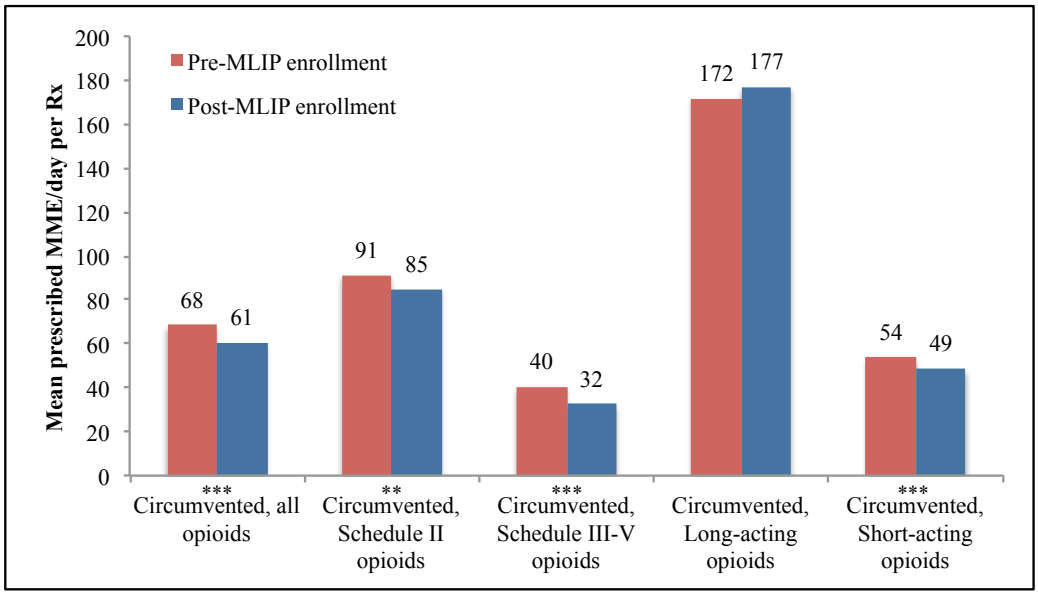
Pre-MLIP enrollment				**Post-MLIP enrollment**			
Rank	**Freq.**	**%**	**Product**	**Rank**	**Freq.**	**%**	**Product**
1	23,312	45.2	Oxycodone IR, oral	1	6,540	56.6	Oxycodone IR, oral
2	23,293	45.1	Hydrocodone IR, oral	2	3,775	32.6	Hydrocodone IR, oral
3	1,036	2.0	Hydromorphone IR, oral	3	319	2.8	Hydromorphone IR, oral
4	995	1.9	Codeine IR, oral	9	192	1.7	Oxymorphone IR, oral
5	900	1.7	Propoxyphene IR, oral	10	171	1.5	Tapentadol IR, oral

Note: MLIP=Medicaid lock-in program; Freq=Frequency; IR=Immediate release; LA=Long acting. Post-MLIP enrollment period ranks reflect that specific product's frequency rank in the pre-MLIP enrollment period.

Bivariate analyses of prescription-level opioid dosage showed that the average prescribed MME/day per prescription obtained through circumvention either significantly decreased or did not change after subjects were enrolled in the NC MLIP (Figure 4.6). Among all circumvented opioid fills, the mean MME/day decreased 10% from 68 to 61 MME/day ($p<0.001$) from the pre- to post-MLIP enrollment periods. Similar findings were reported for subsets of circumvented Schedule II, Schedule III-V, and short acting opioid prescriptions. Circumvented long acting opioid products had the highest initial

average MME/day at around 175 MME/day, on average, which did not differ based on MLIP enrollment status.

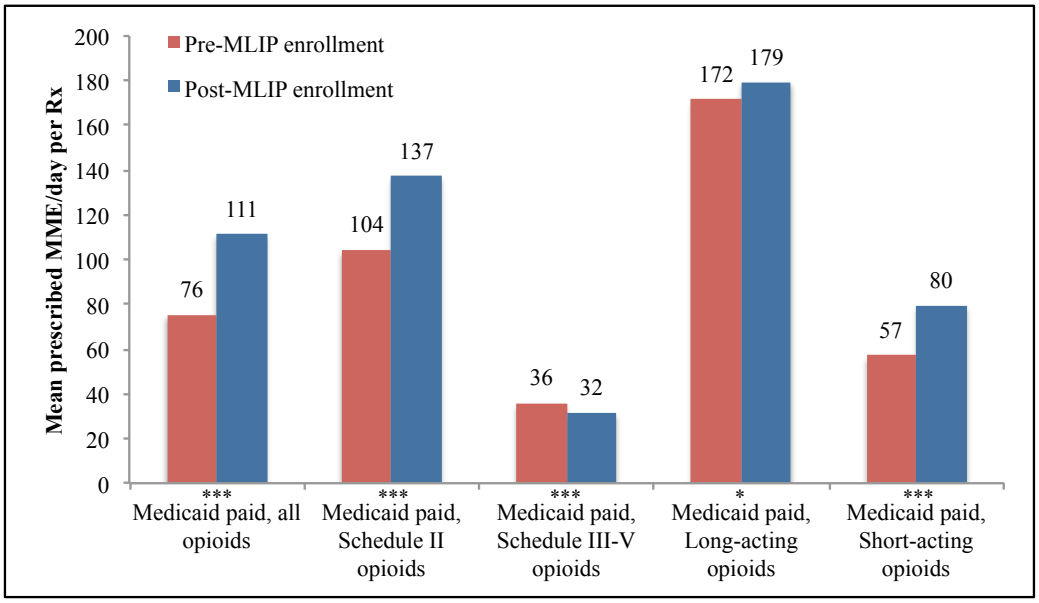
Figure 4.6: Bivariate comparisons of mean prescribed MME/day for circumvented opioid prescriptions, by MLIP enrollment status



Note: MME=Milligram morphine equivalents; MLIP=Medicaid lock-in program; Rx=Prescription.***p<0.001; **p<0.01; *p<0.05

In contrast to the observed bivariate circumvented opioid prescriptions trends, Medicaid paid opioid prescriptions generally experienced a significant increase in mean MME/day per prescription after MLIP enrollment. Among all Medicaid paid opioid prescriptions, mean prescription-level MME/day increased by nearly 50% from 76 to 111 MME/day (p<0.001). A similar increase in post-MLIP MME/day was observed for subsets of Medicaid paid Schedule II and short acting opioid prescriptions. Long acting opioid prescriptions obtained through Medicaid experienced a small but significant increase in mean prescribed MME/day. Only Schedule III-V Medicaid paid opioid prescriptions experienced a decrease in daily opioid dose per prescription. It should be noted that MME/day values were comparable between circumvented and Medicaid paid opioid prescriptions in the pre-MLIP enrollment period.

Figure 4.7: Bivariate comparisons of mean prescribed MME/day for Medicaid paid opioid prescriptions, by MLIP enrollment status



Note: MME=Milligram morphine equivalents; MLIP=Medicaid lock-in program; Rx=Prescription.
***p<0.001; **p<0.01; *p<0.05

4.2.2 Aim 2 Generalized Linear Modeling Findings

4.2.2.1 Aim 2 Generalized Linear Modeling Findings—Schedule II opioid outcome

There was no association between NC MLIP enrollment and the likelihood of a circumvented opioid prescription fill containing a Schedule II opioid (RR=0.96; 95% CI: 0.84, 1.09) compared to a Schedule III-V opioid, controlling for patient- and policy-level covariates (Table 4.10). Among opioid prescriptions obtained by study subjects through the Medicaid benefit, NC MLIP enrollment was associated with a 32% increase in the likelihood of an opioid prescription containing a Schedule II product (95% CI: 1.23, 1.41). The effect of NC MLIP enrollment on opioid prescriptions from all payment sources expectedly fell between these two point estimates. Overall, opioid prescriptions were 1.19 times more likely to be written for a Schedule II product after MLIP enrollment, controlling for covariates (95% CI: 1.12, 1.27).

Table 4.10: Generalized linear modeling estimates for the likelihood of an opioid Rx containing a Schedule II opioid product versus a Schedule III-V product

	Circumvented Opioid Fills			Medicaid-Paid Opioid Fills			Total Opioid Fills		
Variable	**RR**	**(95% CI)**	**P-value**	**RR**	**(95% CI)**	**P-value**	**RR**	**(95% CI)**	**P-value**
Key independent variable									
MLIP enrollment	0.96	(0.84, 1.09)	0.521	1.32	(1.23, 1.41)	<0.001	1.19	(1.12, 1.27)	<0.001
MLIP policy variables									
MLIP enrollment * month	1.00	(0.99, 1.01)	0.618	1.01	(1.00, 1.02)	0.001	1.01	(1.00, 1.01)	0.043
MLIP enrollment delay	1.00	(0.88, 1.12)	0.940	1.07	(1.02, 1.12)	0.010	1.06	(1.01, 1.11)	0.014
MLIP enrollment delay * month	1.01	(0.99, 1.02)	0.353	1.01	(1.00, 1.02)	0.004	1.01	(1.00, 1.02)	0.006
Month	1.01	(1.00, 1.03)	0.023	1.01	(1.00, 1.01)	0.012	1.01	(1.00, 1.01)	0.001
MLIP policy period	1.03	(0.91, 1.17)	0.597	0.92	(0.88, 0.97)	0.001	0.93	(0.89, 0.97)	0.002
MLIP policy period * month	0.98	(0.97, 1.00)	0.036	0.99	(0.99, 1.00)	0.031	0.99	(0.99, 1.00)	0.019
MLIP eligibility route									
Opioid use	0.93	(0.76, 1.13)	0.442	0.93	(0.83, 1.05)	0.237	0.93	(0.83, 1.05)	0.227
Benzodiazepine use	0.89	(0.69, 1.15)	0.369	0.84	(0.67, 1.06)	0.144	0.85	(0.69, 1.04)	0.122
Pharmacy use	1.02	(0.91, 1.13)	0.775	0.90	(0.85, 0.95)	<0.001	0.90	(0.85, 0.96)	0.001
No eligibility criteria met	1.00	(0.76, 1.31)	0.995	0.95	(0.81, 1.12)	0.563	0.95	(0.81, 1.12)	0.537
Predisposing characteristics									
Age	1.002	(1.00, 1.01)	0.353	1.006	(1.00, 1.01)	<0.001	1.006	(1.00, 1.01)	<0.001
Female	0.81	(0.74, 0.89)	<0.001	0.86	(0.82, 0.91)	<0.001	0.86	(0.81, 0.91)	<0.001
Race (White referent)									
Black	1.12	(1.00, 1.26)	0.051	1.09	(1.02, 1.16)	0.008	1.09	(1.02, 1.17)	0.010
Other	1.12	(0.95, 1.32)	0.166	1.03	(0.94, 1.14)	0.494	1.05	(0.95, 1.16)	0.380
Enabling characteristics									
Metropolitan residence	0.91	(0.82, 1.01)	0.081	0.92	(0.86, 0.98)	0.015	0.92	(0.86, 0.98)	0.014
County pharmacy supply (<10 referent)									
11-25	0.96	(0.85, 1.10)	0.571	0.98	(0.90, 1.06)	0.566	0.97	(0.90, 1.05)	0.513
26-50	0.97	(0.85, 1.09)	0.586	0.95	(0.88, 1.03)	0.210	0.95	(0.88, 1.03)	0.200
51-100	1.10	(0.96, 1.26)	0.183	1.05	(0.96, 1.14)	0.321	1.05	(0.96, 1.15)	0.273
>100	0.90	(0.74, 1.08)	0.254	0.94	(0.85, 1.05)	0.255	0.92	(0.83, 1.03)	0.161
Border county	0.90	(0.81, 0.99)	0.031	0.93	(0.88, 0.99)	0.022	0.93	(0.87, 0.98)	0.010
Need characteristics									
Chronic non-cancer pain	1.26	(0.97, 1.63)	0.087	1.17	(1.00, 1.37)	0.045	1.18	(1.02, 1.38)	0.031
Anxiety disorder	1.00	(0.90, 1.10)	0.960	0.96	(0.91, 1.02)	0.163	0.97	(0.91, 1.02)	0.228
Substance abuse disorder	1.03	(0.94, 1.12)	0.558	1.09	(1.04, 1.15)	0.001	1.07	(1.02, 1.13)	0.009
Depression	1.11	(1.01, 1.22)	0.032	1.03	(0.97, 1.09)	0.288	1.04	(0.98, 1.10)	0.180
Other mental illness	0.97	(0.88, 1.07)	0.527	0.95	(0.90, 1.00)	0.062	0.95	(0.90, 1.00)	0.070
Charlson Comorbidity Index (0 referent)									
1	1.04	(0.93, 1.16)	0.492	0.98	(0.91, 1.04)	0.491	0.99	(0.92, 1.06)	0.711
≥2	1.15	(1.02, 1.30)	0.026	1.03	(0.96, 1.10)	0.395	1.05	(0.98, 1.13)	0.158
Prescription drug burden	1.00	(0.99, 1.00)	0.413	1.00	(1.00, 1.00)	0.592	1.00	(1.00, 1.00)	0.552

Note: Rx=Prescription; RR=Relative risk; CI=Confidence interval; MLIP=Medicaid lock-in program. All GLM models used a Poisson distribution, log link, and cluster-robust standard errors. The circumvented model included 19,778 fills (1,527 subjects); Medicaid paid included 78,465 fills (1,634 subjects); total included 98,243 fills (1,646 subjects).

Few patient characteristics were predictive of the likelihood of Schedule II opioid receipt in the context of circumvention behavior. Female subjects were 19% less likely for a circumvented opioid fill to be written for a Schedule II product compared to males, all else being equal (95% CI: 0.74, 0.89). Black subjects had a strong, but not statistically significant, positive association with the probability of a circumvented opioid prescription containing a Schedule II product (RR=1.12; 95% CI: 1.00, 1.26). Subjects residing in a border county in North Carolina were significantly less likely for a circumvented fill to contain a Schedule II product compared to those living in the interior of the state (RR=0.90; 95% CI: 0.81, 0.99). Finally, subjects with a baseline diagnosis of depression and high physical comorbidity burden had a significantly positive association with the dichotomous prescription-level Schedule II opioid outcome.

Many patient- and policy-level covariates were associated with Schedule II opioid prescribing in the context of Medicaid covered opioid use behavior. Compared to males, female sex was again associated with lower likelihood of a Medicaid paid opioid prescription being written for a Schedule II product (RR=0.86; 95% CI: 0.82, 0.91). Residence in a rural county and border county were significantly associated with an 8% (95% CI: 0.86, 0.98) and 7% (95% CI: 0.88, 0.99) decrease in the likelihood of a Medicaid paid opioid prescription containing a Schedule II product, respectively. Increased age (RR=1.006; 95% CI: 1.00, 1.01) and Black race (RR=1.09; 95% CI: 1.02, 1.16) were predictive of a higher likelihood of Schedule II opioid prescribing among the Medicaid paid opioid prescription subset. Among opioid use occurring within the NC Medicaid benefit, subjects with a chronic noncancer pain diagnosis (RR=1.17; 95% CI: 1.00, 1.37) and substance abuse disorder (RR=1.09; 95% CI: 1.04, 1.15) were significantly more likely to fill a Schedule II opioid compared to those without such baseline diagnoses. With regard to policy covariates, a Medicaid paid opioid fill occurring within a period of delayed MLIP enrollment was 7% more likely to be written for a Schedule II product, while MLIP eligibility due to high unique pharmacy user was predictive of lower likelihood of a Medicaid paid opioid prescription being written for a Schedule II product.

4.2.2.2 Aim 2 Generalized Linear Modeling Findings—Long-acting opioid outcome

Opioid prescriptions obtained by subjects through circumvention were more than 40% less likely to contain a long acting opioid product after they were enrolled in the NC MLIP (RR=0.58; 95% CI: 0.40, 0.85), controlling for covariates (Table 4.11). However, opioid prescriptions that subjects paid for using the NC Medicaid benefit were 2.15 times more likely to be written for long acting opioid products after NC MLIP (RR=2.15; 95% CI: 1.86, 2.48). Overall, NC MLIP enrollment was associated with a 55% increase in the probability of receiving a long acting opioid when examining all opioid prescriptions from all payment sources (RR=1.55; 95% CI: 1.35, 1.79).

Table 4.11: Generalized linear modeling estimates for the likelihood of an opioid Rx containing a long-acting opioid product versus a short-acting opioid product

	Circumvented Opioid Fills			Medicaid-Paid Opioid Fills			Total Opioid Fills		
Variable	**RR**	**(95% CI)**	**P-value**	**RR**	**(95% CI)**	**P-value**	**RR**	**(95% CI)**	**P-value**
Key independent variable									
MLIP enrollment	0.58	(0.40, 0.85)	0.005	2.15	(1.86, 2.48)	<0.001	1.55	(1.35, 1.79)	<0.001
MLIP policy variables									
MLIP enrollment * month	1.02	(0.99, 1.06)	0.207	1.03	(1.01, 1.04)	<0.001	1.02	(1.01, 1.04)	0.001
MLIP enrollment delay	0.84	(0.61, 1.18)	0.316	0.99	(0.89, 1.11)	0.903	0.99	(0.89, 1.11)	0.856
MLIP enrollment delay * month	1.02	(0.97, 1.07)	0.485	1.04	(1.02, 1.06)	<0.001	1.03	(1.01, 1.05)	0.001
Month	1.00	(0.96, 1.04)	0.997	1.00	(0.99, 1.01)	0.936	1.00	(0.99, 1.01)	0.603
MLIP policy period	1.35	(0.98, 1.86)	0.069	0.88	(0.79, 0.99)	0.029	0.90	(0.81, 1.00)	0.046
MLIP policy period * month	1.00	(0.95, 1.04)	0.913	0.98	(0.97, 1.00)	0.012	0.98	(0.97, 1.00)	0.039
MLIP eligibility route									
Opioid use	0.73	(0.45, 1.19)	0.212	0.91	(0.68, 1.22)	0.523	0.88	(0.66, 1.17)	0.365
Benzodiazepine use	0.76	(0.37, 1.55)	0.447	0.65	(0.42, 1.00)	0.052	0.65	(0.42, 0.99)	0.044
Pharmacy use	0.88	(0.66, 1.18)	0.401	0.70	(0.62, 0.80)	<0.001	0.69	(0.60, 0.79)	<0.001
No eligibility criteria met	0.65	(0.24, 1.80)	0.409	0.91	(0.60, 1.37)	0.651	0.85	(0.55, 1.30)	0.443
Predisposing characteristics									
Age	1.007	(0.99, 1.02)	0.322	1.015	(1.01, 1.02)	<0.001	1.017	(1.01, 1.02)	<0.001
Female	0.83	(0.61, 1.13)	0.231	0.86	(0.76, 0.98)	0.021	0.87	(0.76, 1.00)	0.048
Race (White referent)									
Black	0.98	(0.68, 1.42)	0.913	0.97	(0.81, 1.15)	0.689	0.95	(0.79, 1.15)	0.619
Other	0.95	(0.53, 1.70)	0.874	1.08	(0.86, 1.36)	0.486	1.06	(0.82, 1.36)	0.667
Enabling characteristics									
Metropolitan residence	0.86	(0.60, 1.23)	0.411	0.86	(0.74, 1.00)	0.051	0.86	(0.73, 1.01)	0.071
County pharmacy supply (<10 referent)									
11-25	0.90	(0.58, 1.38)	0.619	0.98	(0.83, 1.17)	0.851	0.97	(0.81, 1.17)	0.757
26-50	0.99	(0.65, 1.50)	0.949	1.09	(0.90, 1.31)	0.376	1.06	(0.87, 1.29)	0.571
51-100	1.14	(0.73, 1.78)	0.563	1.12	(0.91, 1.38)	0.299	1.11	(0.89, 1.38)	0.346
>100	0.81	(0.48, 1.38)	0.435	1.15	(0.92, 1.44)	0.210	1.08	(0.85, 1.37)	0.519
Border county	1.07	(0.80, 1.44)	0.633	0.90	(0.79, 1.02)	0.109	0.91	(0.80, 1.04)	0.179
Need characteristics									
Chronic non-cancer pain	5.08	(1.70, 15.17)	0.004	2.35	(1.39, 3.95)	0.001	2.47	(1.42, 4.28)	0.001
Anxiety disorder	0.86	(0.62, 1.18)	0.343	0.83	(0.74, 0.94)	0.003	0.83	(0.73, 0.95)	0.006
Substance abuse disorder	1.24	(0.93, 1.66)	0.136	1.18	(1.05, 1.33)	0.007	1.16	(1.02, 1.32)	0.020
Depression	1.21	(0.91, 1.62)	0.193	1.07	(0.94, 1.22)	0.283	1.08	(0.94, 1.23)	0.295
Other mental illness	0.92	(0.70, 1.22)	0.562	0.94	(0.83, 1.06)	0.289	0.93	(0.81, 1.06)	0.263
Charlson Comorbidity Index (0 referent)									
1	0.83	(0.57, 1.22)	0.337	0.93	(0.80, 1.08)	0.332	0.91	(0.78, 1.07)	0.272
≥2	1.20	(0.83, 1.73)	0.338	0.99	(0.85, 1.16)	0.926	1.02	(0.86, 1.21)	0.817
Prescription drug burden	0.99	(0.98, 1.01)	0.281	1.00	(0.99, 1.01)	0.928	1.00	(0.99, 1.01)	0.779

Note: Rx=Prescription; RR=Relative risk; CI=Confidence interval; MLIP=Medicaid lock-in program. All GLM models used a Poisson distribution, log link, and cluster-robust standard errors. The circumvented model included 19,778 fills (1,527 subjects); Medicaid paid included 78,465 fills (1,634 subjects); total included 98,243 fills (1,646 subjects).

Among circumvented opioid prescription fills, only one patient-level characteristic was predictive of receiving a long acting opioid product. Circumvented opioid prescriptions obtained by subjects with a baseline diagnosis of chronic noncancer pain were over five times more likely to contain a long acting opioid compared to subjects with no history of chronic pain (RR=5.08; 95% CI: 1.70, 15.17).

In the context of Medicaid paid opioid prescriptions, multiple covariates were significantly associated with an opioid prescription written for a long acting product. Similarly to the Schedule II outcome discussed previously, female subjects were 14% less likely to fill a long acting opioid product in the context of Medicaid covered opioid use (RR=0.86; 95% CI: 0.76, 0.98) compared to males. Subjects residing in a metropolitan county showed a strong negative association with the outcome, but this was not statistically significant. Medicaid paid opioid prescriptions received by subjects who met MLIP eligibility due to high pharmacy use were 30% less likely to contain a long acting opioid product (RR=0.70; 95% CI: 0.62, 0.82). As patient age increased, the likelihood of a Medicaid paid opioid prescription being written for a long acting product also increased (RR=1.015; 95% CI: 1.01, 1.02). Both a baseline chronic noncancer pain diagnosis (RR=2.35; 95% CI: 1.39, 3.95) and substance abuse disorder (RR=1.18; 95% CI: 1.05, 1.33) were associated with an increased probability of a Medicaid paid opioid prescription containing a long acting preparation, while an anxiety disorder diagnosis had an opposite effect (RR=0.83; 95% CI: 0.74, 0.84). Notably, a subject's MLIP enrollment delay was not associated with the probability of receiving a long acting opioid within the NC Medicaid benefit.

4.2.2.3 Aim 2 Generalized Linear Modeling Findings—Mean MME/day outcome

Finally, Table 4.12 reports GLM estimates of average marginal effect of MLIP enrollment and covariates on average prescribed daily opioid dose, measured as mean prescribed MME/day. In the context of circumvented opioid use, NC MLIP enrollment was not associated with a prescription's mean daily opioid dose (Marginal effect=2.11 MME/day; 95% CI: -6.82, 11.05), when controlling for patient and policy covariates. However, opioid prescriptions obtained through NC Medicaid had an increased prescribed daily opioid dose of 55.87 MME/day after NC MLIP enrollment compared to Medicaid paid opioid prescriptions filled prior to MLIP enrollment (95% CI: 38.33, 73.41).

Table 4.12: Generalized linear modeling estimates of average prescribed MME/day per opioid prescription

	Circumvented Opioid Fills			Medicaid-Paid Opioid Fills			Total Opioid Fills		
Variable	**ME**	**(95% CI)**	**P-value**	**ME**	**(95% CI)**	**P-value**	**ME**	**(95% CI)**	**P-value**
Key independent variable									
MLIP enrollment	2.11	(-6.82, 11.05)	0.643	55.87	(38.33, 73.41)	<0.001	33.12	(21.03, 45.22)	<0.001
MLIP policy variables									
MLIP enrollment * month	0.43	(-0.35, 1.21)	0.283	2.60	(1.48, 3.72)	<0.001	1.85	(0.91, 2.79)	<0.001
MLIP enrollment delay	3.54	(-5.29, 12.37)	0.432	6.98	(1.39, 12.57)	0.014	6.95	(1.75, 12.16)	0.009
MLIP enrollment delay * month	0.94	(-0.54, 2.42)	0.213	3.19	(1.93, 4.46)	<0.001	2.61	(1.49, 3.73)	<0.001
Month	-0.68	(-1.68, 0.33)	0.188	0.32	(-0.17, 0.81)	0.199	0.20	(-0.27, 0.67)	0.400
MLIP policy period	-2.12	(-11.41, 7.18)	0.655	-12.18	(-18.75 , -5.61)	<0.001	-11.77	(-17.99 , -5.55)	<0.001
MLIP policy period * month	0.25	(-0.95, 1.45)	0.684	-2.23	(-3.40 , -1.06)	<0.001	-1.64	(-2.72 , -0.57)	0.003
MLIP eligibility route									
Opioid use	-3.04	(-19.21, 13.13)	0.712	4.11	(-11.48, 19.71)	0.605	2.45	(-12.25, 17.15)	0.744
Benzodiazepine use	-4.02	(-22.85, 14.81)	0.676	0.99	(-23.98, 25.96)	0.938	-1.85	(-23.49, 19.78)	0.867
Pharmacy use	-2.33	(-9.43, 4.77)	0.520	-23.54	(-36.58 , -10.50)	<0.001	-21.40	(-33.40 , -9.39)	<0.001
No eligibility criteria met	-8.08	(-26.26, 10.09)	0.383	-4.38	(-31.52, 22.75)	0.752	-6.15	(-30.08, 17.77)	0.614
Predisposing characteristics									
Age	0.39	(0.08, 0.70)	0.012	1.03	(0.67, 1.40)	<0.001	0.96	(0.63, 1.30)	<0.001
Female	-10.13	(-19.43 , -0.82)	0.033	-10.21	(-18.63 , -1.79)	0.018	-9.72	(-17.83 , -1.61)	0.019
Race (White referent)									
Black	-0.73	(-7.97, 6.51)	0.843	-7.32	(-15.50, 0.86)	0.079	-6.70	(-14.29, 0.90)	0.084
Other	-3.10	(-14.86, 8.67)	0.606	-0.31	(-16.37, 15.74)	0.970	-0.14	(-14.58, 14.30)	0.985
Enabling characteristics									
Metropolitan residence	-4.50	(-12.94, 3.94)	0.296	-0.78	(-10.75, 9.20)	0.879	-0.95	(-10.19, 8.29)	0.840
County pharmacy supply (<10 referent)									
11-25	-1.24	(-10.88, 8.39)	0.800	-10.10	(-21.57, 1.37)	0.084	-8.52	(-19.16, 2.12)	0.117
26-50	0.91	(-9.40, 11.21)	0.863	-1.88	(-16.49, 12.73)	0.801	-1.79	(-15.13, 11.56)	0.793
51-100	-0.08	(-10.48, 10.31)	0.988	-6.51	(-19.53, 6.50)	0.327	-5.48	(-17.55, 6.59)	0.373
>100	-7.84	(-16.61, 0.94)	0.080	-12.06	(-26.11, 1.99)	0.092	-12.59	(-24.86 , -0.31)	0.044
Border county	2.56	(-5.52, 10.64)	0.535	-1.14	(-9.64, 7.37)	0.793	-0.78	(-8.64, 7.07)	0.845
Need characteristics									
Chronic non-cancer pain	13.52	(5.70, 21.34)	0.001	12.29	(1.37, 23.21)	0.027	13.76	(4.40, 23.12)	0.004
Anxiety disorder	-3.32	(-10.47, 3.83)	0.363	0.07	(-8.97, 9.12)	0.987	-0.60	(-8.82, 7.62)	0.886
Substance abuse disorder	2.81	(-3.33, 8.95)	0.370	7.24	(-1.76, 16.25)	0.115	5.89	(-2.26, 14.03)	0.157
Depression	1.76	(-4.95, 8.46)	0.608	3.26	(-4.64, 11.16)	0.419	2.82	(-4.47, 10.11)	0.448
Other mental illness	-0.66	(-7.16, 5.84)	0.842	-3.14	(-11.76, 5.49)	0.476	-2.99	(-10.92, 4.94)	0.460
Charlson Comorbidity Index (0 referent)									
1	5.26	(-2.60, 13.12)	0.190	3.32	(-6.75, 13.39)	0.518	4.50	(-5.02, 14.02)	0.354
≥2	15.72	(6.64, 24.80)	0.001	6.36	(-3.49, 16.20)	0.206	8.63	(-0.33, 17.60)	0.059
Prescription drug burden	-0.48	(-0.82 , -0.15)	0.005	-0.43	(-0.94, 0.07)	0.090	-0.45	(-0.90, 0.00)	0.051

Note: Rx=Prescription; ME=Marginal effect; CI=Confidence interval; MLIP=Medicaid lock-in program. All three GLM models specified an inverse Gaussian distribution, log link, and cluster-robust standard errors. The circumvented model included 19,691 fills (1,526 subjects), the Medicaid paid model included 78,429 fills (1,634 subjects), the total model included 98,120 fills (1,646 subjects). A total of 123 opioid fills were excluded from analysis due to parenteral or rectal route not amenable to MME measure assessment.

Among circumvented opioid prescription fills, average MME/day per prescription increased significantly as age increased (ME: 0.39 MME/day; 95% CI: 0.08, 0.70). Circumvented opioid prescriptions filled by female subjects had 10.13 fewer mean MME/day compared to those circumvented by male subjects (95% CI: -19.43, -0.82). Similar to findings for the binary Schedule II and long acting product prescription-level outcomes, a baseline diagnosis of chronic noncancer pain was associated with an increase in mean prescribed MME/day per circumvented prescription of 13.52 (95% CI: 5.70, 21.34). Subjects with high physical comorbidity burden received circumvented opioid prescriptions with significantly higher average MME/day (ME=15.72 MME/day; 95% CI: 6.64, 24.80). However, prescription drug burden—another marker of comorbidity burden—exhibited a small, but significant, negative association with mean MME/day per circumvented prescription (ME=-0.48; 95% CI: -0.82, -0.15). MLIP enrollees who were eligible

Increasing subject age (ME=1.03 MME/day; 95% CI: 0.67, 1.40), female sex (ME=-10.21 MME/day; 95% CI: -18.63, -1.79), and baseline chronic pain diagnosis (ME=12.29 MME/day; 95% CI: 1.37, 23.21) were associated with prescribed daily opioid dosage per opioid Medicaid paid prescription similarly to the effects observed in the subset of circumvented prescriptions. Medicaid paid opioid prescriptions obtained during a period of delayed MLIP enrollment provided 6.98 MME/day more than prescriptions filled outside of an enrollment delay (95% CI: 1.39, 12.57). Subjects eligible for the MLIP due to high use of pharmacies obtained Medicaid covered opioid prescriptions with significantly smaller prescribed daily opioid doses (ME=-23.54 MME/day; 95% CI: -36.58, -10.50).

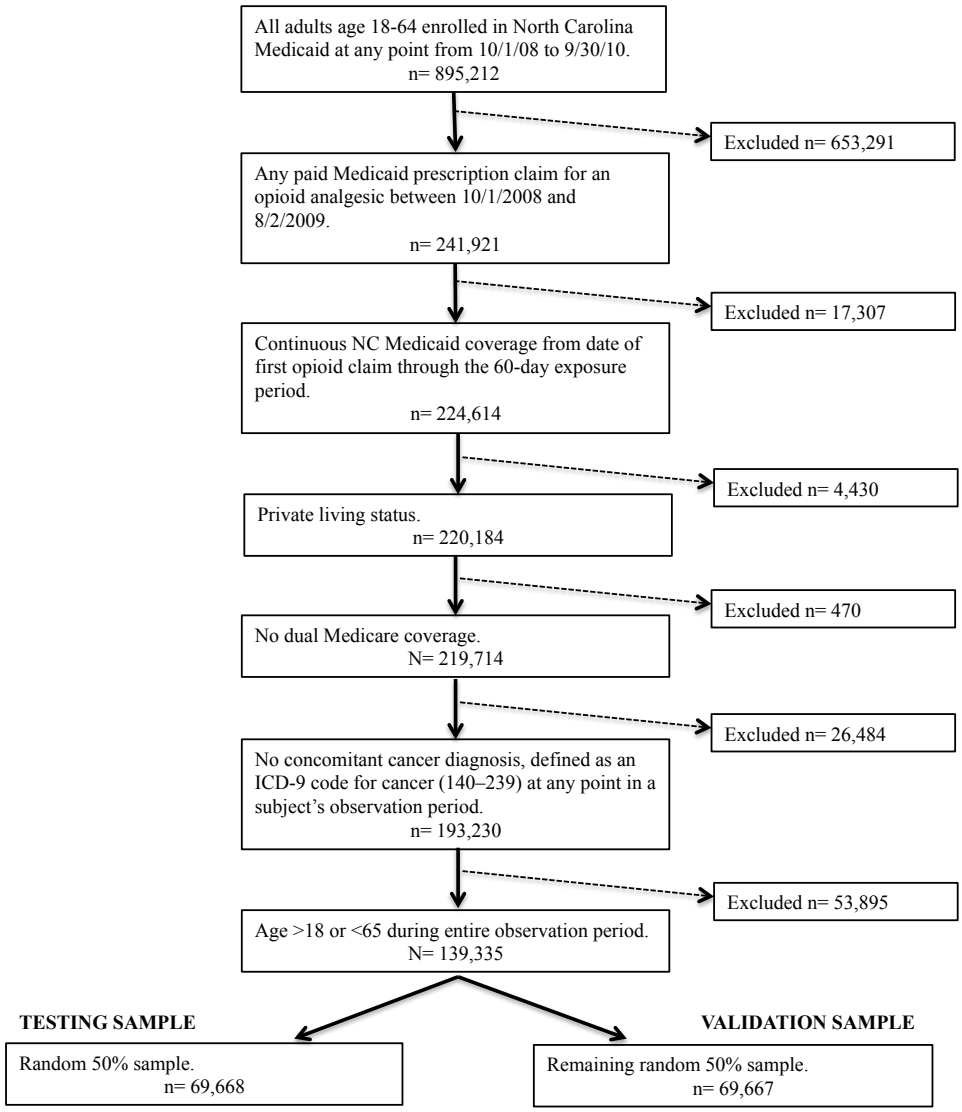
4.3 AIM 3 RESULTS

4.3.1 Aim 3 Descriptive Analysis Findings

The Aim 3 analytic cohort included 139,355 NC Medicaid beneficiaries, which were randomly assigned into testing and validation samples comprised of 69,668 and 69,667 subjects, respectively (Figure 4.8). Subjects were selected from an initial pool of 895,212 adults with NC Medicaid coverage at some point during the study period of 10/1/08 to 9/30/10. Nearly 242,000 of these subjects recorded a Medicaid claim for an opioid analgesic prescription during the observation period for index opioid use

from 10/1/08 to 8/2/09. Over 17,000 subjects were excluded due to a lack of continuous Medicaid coverage for the entire 60-day exposure assessment period following the index opioid fill. An additional 4,430 and 470 subjects were excluded due to non-private living status and dual Medicare coverage, respectively. Over 26,000 subjects recorded a cancer diagnosis during their study observation and were excluded from analysis. Lastly, 53,895 subjects were dropped from the study for being less than 18 or greater than 64 years of age at some point during their observation.

Figure 4.8: Aim 3 analytic cohort selection



The mean age of the Aim 3 cohort was 34.3 years (Table 4.13). Seventy-seven percent of subjects were female, 55.6% were White race, and 37% were of Black race. On average, subjects contributed 275 days of follow-up observation out of a maximum of 365 days of follow-up time. Overall, Aim 3 subjects received an average of 2.1 opioid prescriptions and used 1.2 unique dispensing pharmacies during the 60-day exposure period following their index opioid fill. The mean MME/day for the 60-day exposure period was 22.3 MME/day, while the average daily APAP exposure from opioid/APAP combination products was 569mg APAP/day. A total of 376 subjects, which represented 0.3% of the full Aim 3 cohort, experienced the primary outcome of an unintentional opioid overdose during follow-up, with an average time to event of 170 days. For the secondary outcome measures, 172 subjects experienced an acetaminophen overdose. A total of 2,161 (1.6%) subjects experienced an unintentional overdose event from any drug substance. Both secondary overdose outcome measures had a mean time to event of 155-160 days. Over 4,500 subjects (3.2%) received a diagnosis of an opioid use disorder during their follow-up, while 39,533 (28.4%) recorded a substance use disorder diagnosis of any nature. Average time to diagnosis of substance use disorder secondary outcomes was around 120 days. Random assignment to the testing and validation samples resulted in no statistically significant differences between these groups with regard to any demographic, exposure, or outcome measure.

Table 4.13: Summary statistics for the Aim 3 cohort, by testing and validation sample subsets

	Overall (n=139,335)	**Testing sample (n=69,668)**	**Validation sample (n=69,667)**	**p-value**
Demographic characteristics				
Age, mean (SD)	34.3 (12.2)	34.3 (12.1)	34.3 (12.2)	0.984
Female, n (%)	107172 (76.9%)	53499 (76.8%)	53673 (77.0%)	0.267
Race, n (%)				
White	77414 (55.6%)	38627 (55.4%)	38787 (55.7%)	0.387
Black	51364 (36.9%)	25721(36.9%)	25643 (36.8%)	0.667
Other/unknown	10557 (7.6%)	5320 (7.6%)	5237 (7.5%)	0.401
Days of follow-up, mean (SD)	275 (129)	275 (129)	276 (129)	0.780
Opioid exposures, mean (SD)				
Opioid prescription count	2.1 (1.6)	2.1 (1.6)	2.1 (1.6)	0.255
Pharmacy count	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)	0.305
Average MME/day	22.3 (70.1)	22.5 (69.5)	22.0 (70.7)	0.222
Average APAP mg/day	569 (780)	571 (783)	567 (777)	0.256
Primary outcome event, n (%)				
Unintentional overdose, opioid	376 (0.3%)	202 (0.3%)	174 (0.3%)	0.148
Days to event, mean (SD)	170 (100)	164 (101)	176 (99)	0.246
Secondary outcome events, n (%)				
Unintentional overdose, APAP	172 (0.1%)	82 (0.1%)	90 (0.1%)	0.542
Days to event, mean (SD)	155 (100)	147 (103)	162 (98)	0.325
Unintentional overdose, any drug	2161 (1.6%)	1040 (1.5%)	1121 (1.6%)	0.079
Days to event, mean (SD)	159 (102)	156 (103)	162 (101)	0.181
Opioid use disorder	4525 (3.2%)	2284 (3.3%)	2241 (3.2%)	0.516
Days to event, mean (SD)	121 (111)	119 (110)	124 (112)	0.098
Any substance use disorder	39533 (28.4%)	19713 (28.3%)	19820 (28.4%)	0.524
Days to event, mean (SD)	118 (101)	118 (101	119 (101)	0.153

Note: SD=Standard deviation; MME=Milligram morphine equivalent; APAP=Acetaminophen; mg=Milligrams. Reported percentages refer to the proportion of the total n represented within that column.

4.3.2 Aim 3 Testing Phase Findings

AUCs from survival ROC models are presented first for each individual opioid exposure and outcome pairing to determine the overall discriminatory capability of each measure in predicting primary and secondary outcome events. After discussing opioid exposure measure AUCs, we then report optimal cutpoints for these measure based on survival ROC findings.

Each opioid exposure and outcome measure pairing demonstrated poor or failed ability to discriminate between subjects who experienced and did not experience the primary and secondary

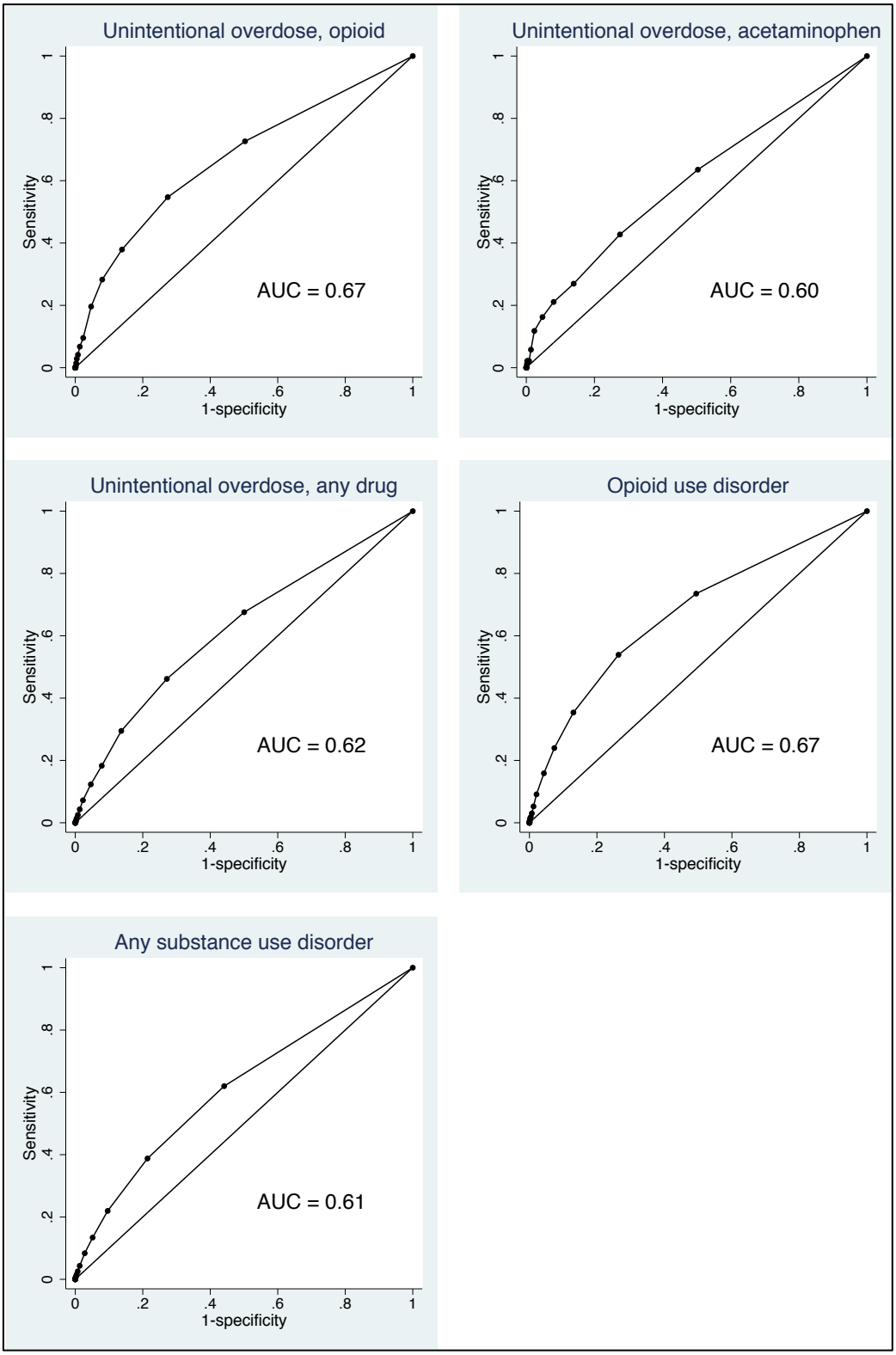
outcomes during follow-up (Figures 4.9 – 4.12). The number of opioid prescriptions received in the 60-day exposure period produced an AUC of 0.67 for the primary outcome of an unintentional opioid overdose event (Figure 4.9). The opioid prescription count measure resulted in AUCs of 0.60-0.67 for the secondary outcomes. Based on pre-determined AUC performance ranges described in the methods chapter (Excellent=0.90-1.00, Good=0.80-0.89, Fair=0.70-0.79, Poor=0.60-0.69, Failed=0.50-0.59), opioid fill count was a poor individual discriminator of relevant clinical outcomes from high-risk opioid use.

The number of unique community and outpatient pharmacies used to obtain an opioid prescription failed to discriminate between subjects at risk of an unintentional opioid overdose, with an AUC of 0.57 (Figure 4.10). The pharmacy count measure also failed to predict the secondary outcomes, with the exception of the opioid use disorder outcome, for which it had poor discriminatory capability (AUC=0.61).

Average MME/day over the 60-day opioid exposure assessment period had similar performance to the opioid fill count measure with regard to the primary outcome (Figure 4.11). Mean MME/day produced an AUC of 0.68 for the unintentional opioid overdose outcome. This exposure measure performed worse for the secondary outcomes, with AUCs ranging from 0.54 for the APAP overdose outcome to 0.64 for the opioid use disorder diagnosis outcome.

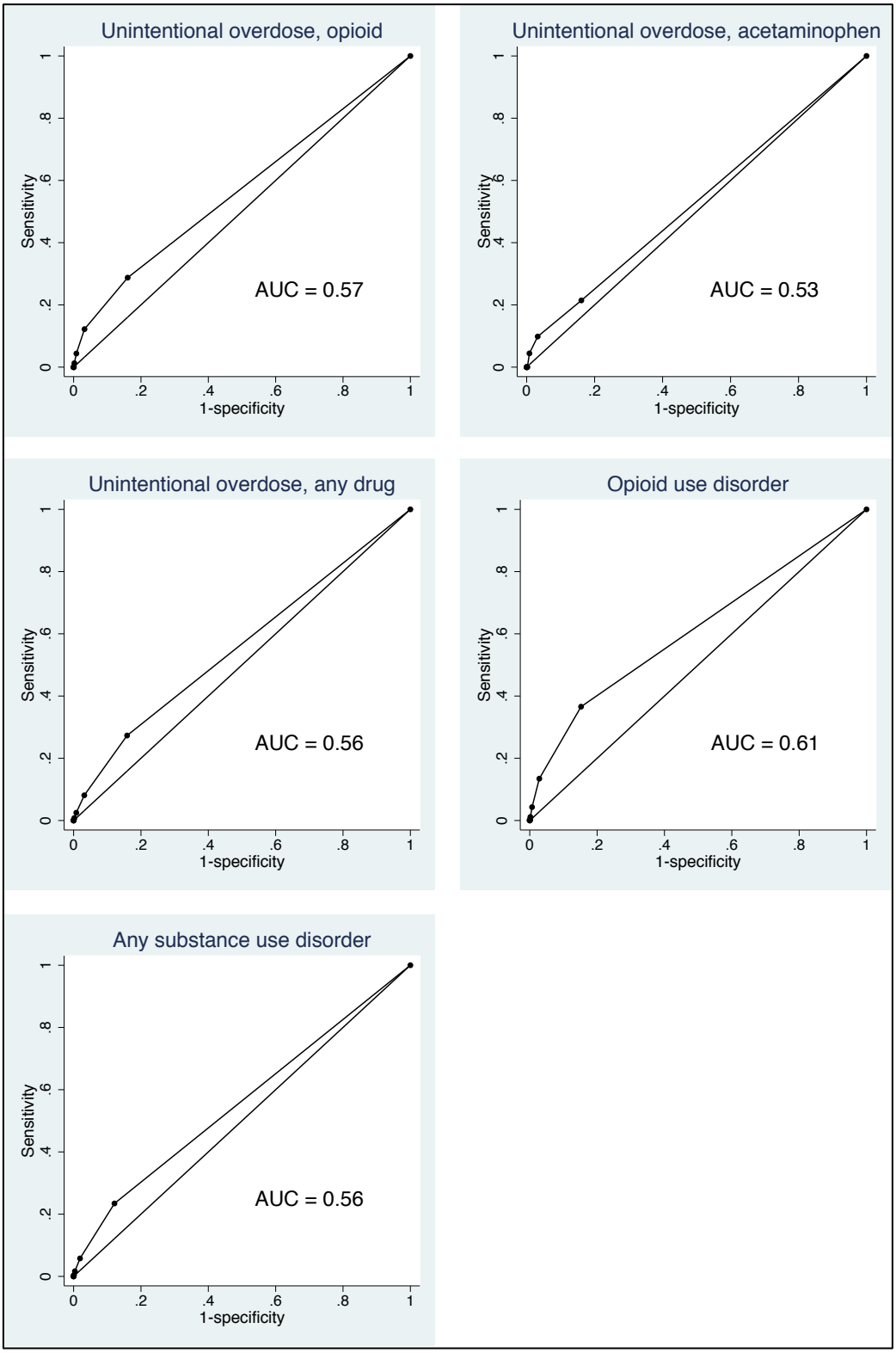
The measure of average APAP dose/day from opioid/APAP combination products nearly failed to discriminate between subjects who had an unintentional opioid overdose during following with an AUC of 0.60 (Figure 4.12). APAP mg/day did fail in its ability to discriminate between patients experiencing each secondary outcome as evidenced by AUCs all less than 0.60.

Figure 4.9: Survival ROC models of the prescription fill count opioid exposure measure



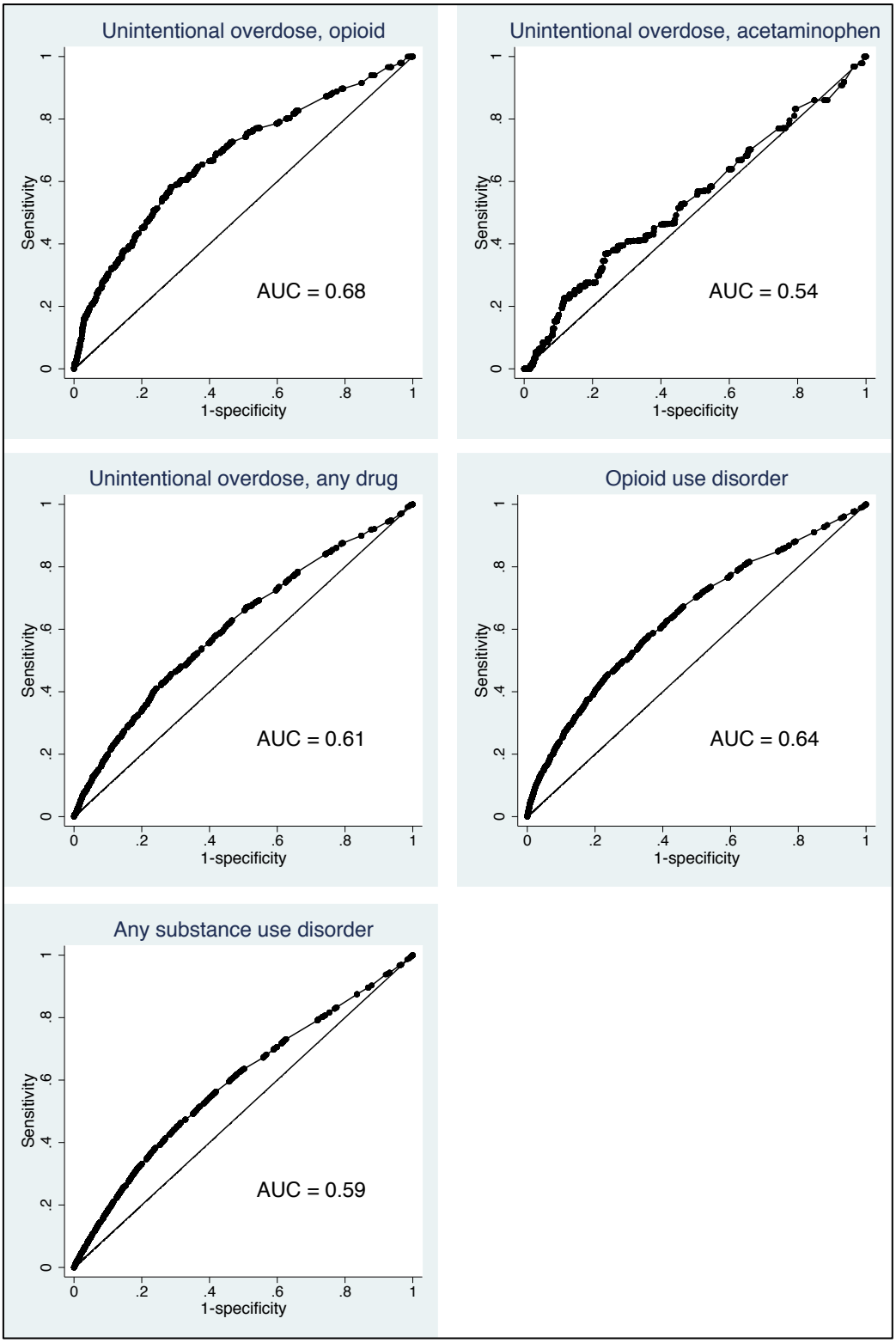
Note: ROC=Receiver operative characteristic; AUC=Area under the curve

Figure 4.10: Survival ROC models of the unique pharmacy count opioid exposure measure



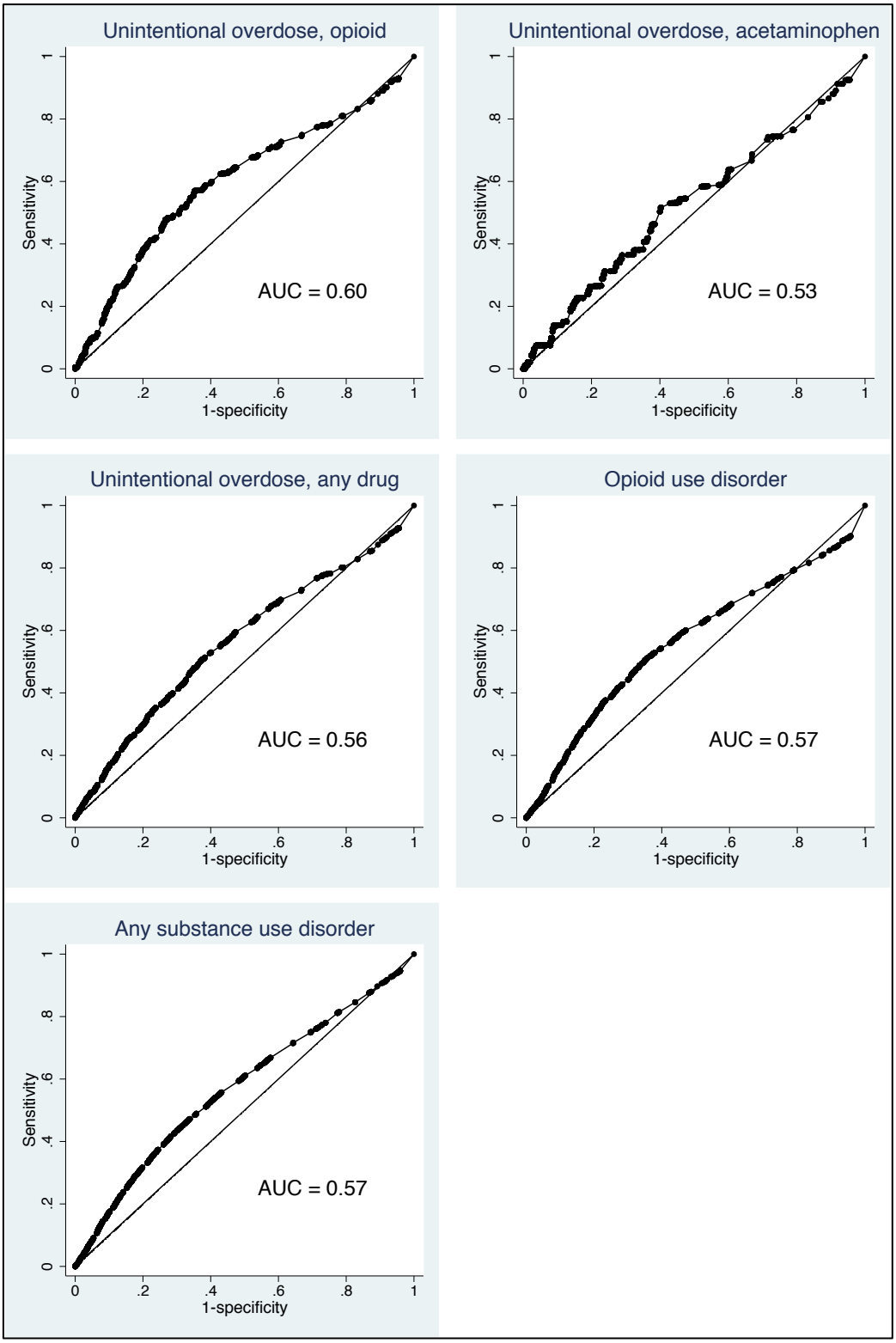
Note: ROC=Receiver operative characteristic; AUC=Area under the curve

Figure 4.11: Survival ROC models of the average MME/day opioid exposure measure



Note: ROC=Receiver operative characteristic; MME=Milligram morphine equivalent; AUC=Area under the curve

Figure 4.12: Survival ROC models of the average APAP mg/day opioid exposure measure



Note: ROC=Receiver operative characteristic; APAP=Acetaminophen; mg=Milligrams; AUC=Area under the curve

The discriminatory performance of opioid exposure measures when modeled together did not improve over the best performing individual measures (Table 4.14). Logistic regression ROC models—which was used for this analysis due to limitations in the survival ROC modeling package disallowing multiple right-hand side variables—found an AUC of 0.70 when modeling opioid fill count and average MME/day simultaneously in the full testing sample. These two measures were combined because they were most predictive of the primary outcome individually. And when restricting to the 42,459 subjects with continuous NC Medicaid coverage for the full 365 days of follow-up, which was done to account for the inability of the logistic models to account for varied observation periods, the combined opioid fill count and average MME/day model achieved an AUC of 0.68 for the primary outcome. These were identical to logistic ROC estimation of the single mean MME/day measure. Adding the pharmacy count and mean APAP mg/day measures to the logistic ROC models for both the full and continuously enrolled testing samples did not contribute any additional discriminatory capability to the model.

Table 4.14: Logistic ROC analysis findings for each individual and combinations of opioid exposure measures in predicting the primary Aim 3 outcome of unintentional opioid overdose

	Area under the curve		
	Survival ROC method (n=69,668)	**Logistic ROC method- Full sample** (n=69,668)	**Logistic ROC method- Cont. enrolled[2]** (n=42,459)
Individual measures[1]			
Opioid fill count	0.67	0.69	0.67
Pharmacy count	0.57	0.57	0.56
Mean MME/day	0.68	0.70	0.68
Mean APAP mg/day	0.60	0.62	0.59
Combinations			
All four exposure measures		0.70	0.68
Opioid fill count + mean MME/day[3]		0.70	0.68

Note: ROC=Receiver operating characteristic; Cont.=Continuously; MME=Milligram morphine equivalent; APAP=Acetaminophen; mg=Milligram.
1. Individual opioid exposure measures were examined to compare similarity, and thus reliability, of the survival ROC method used in primary analysis with the logistic ROC method required to model multiple opioid exposure measures simultaneously.
2. Continuously enrolled referred to the subset of subjects with a full 365 days of follow-up after the 60-day exposure assessment period.
3. Opioid fill count and mean MME/day were selected because they were best performing in survival ROC models

Based on survival ROC model results, the opioid exposure measures of unique pharmacy count and average APAP mg/day failed to predict the primary and secondary outcomes. Additionally, pharmacy counts and mean APAP mg/day measures failed to improve upon the discriminatory capability of the individual and combined opioid prescription counts and mean MME/day measures in ROC models and were disregarded from further examination. For the opioid prescription count and mean MME/day opioid exposure measures, survival ROC model results were analyzed to determine their optimal cutpoints. Survival ROC-derived optimal cutpoints were defined as the value of the exposure measure with jointly maximized sensitivity and specificity in predicting the primary outcome of unintentional opioid overdose event (Table 4.15). Receiving three or more opioid prescription fills and having an average of ≥10 MME/day over the 60-day exposure assessment period were each identified as optimal cutpoints from the ROC output. Appendix Tables 10-29 report comprehensive findings for the number of subjects flagged and the discriminatory performance at varied cutpoints for all four opioid exposure measures. Optimal ROC-derived cutpoints were consistent for each opioid exposure measure across all outcomes.)

Table 4.15: Optimal opioid exposure measure cutpoints from survival ROC models predicting primary outcome of unintentional opioid overdose

	Opioid Rx count	**Mean MME/day**
Optimal ROC cutpoint[1]	≥3 fills	≥10 MME/day
Subjects meeting cutpoint, n (% of total testing sample)	19,166 (27.5%)	23,122 (33.2%)
Primary outcome events, n (% within cutpoint group)	117 (0.6%)	132 (0.6%)
Cutpoint sensitivity	0.55	0.60
Cutpoint specificity	0.73	0.67
Cutpoint joint sensitivity/specificity[1]	0.47	0.48

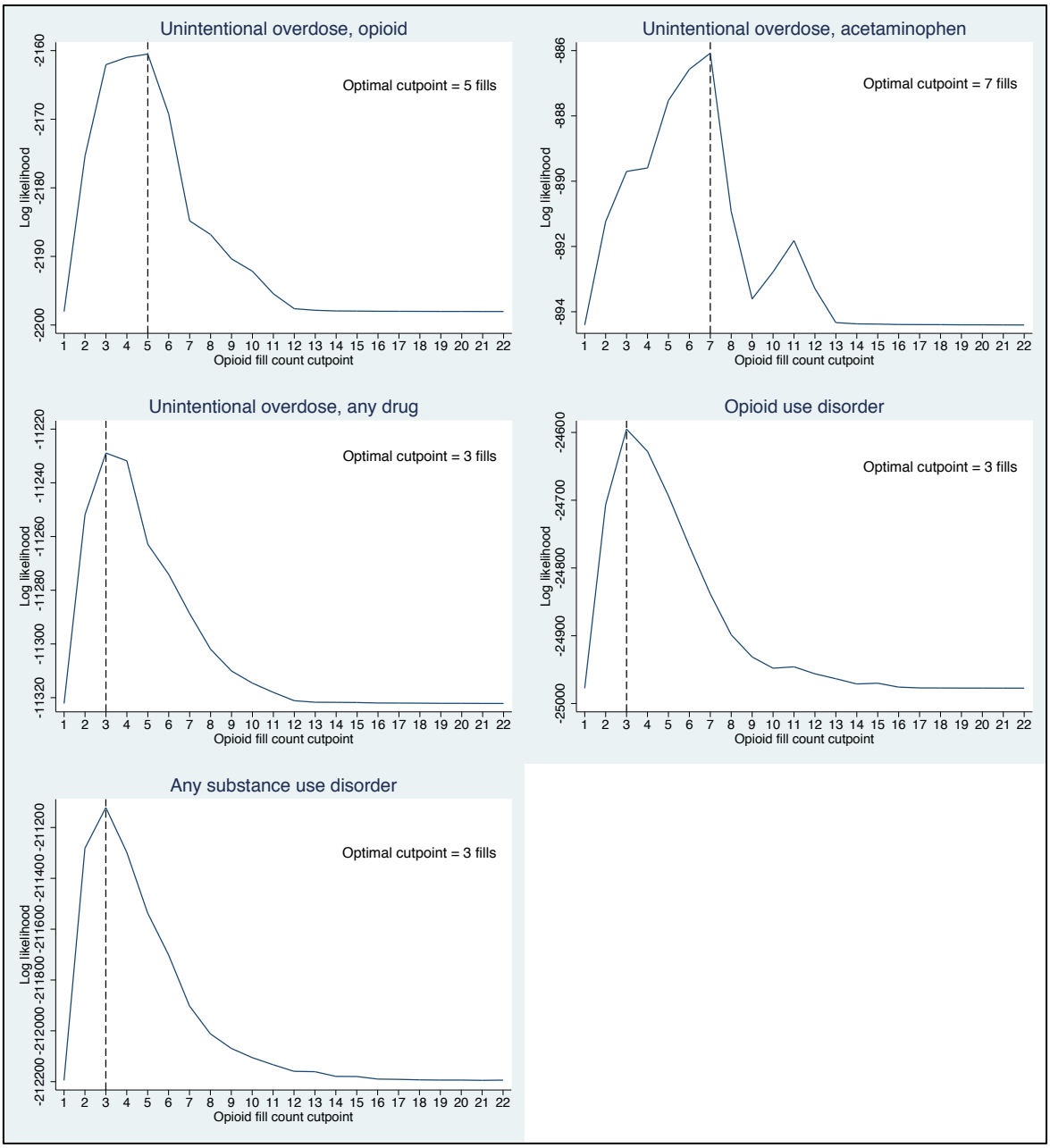
Note: ROC=Receiver operating characteristic; Rx=Prescription; MME=Milligram morphine equivalent; APAP=Acetaminophen; mg=Milligram.
1. The optimal ROC cutpoint was defined as the value of an opioid exposure measure with jointly maximized sensitivity and specificity. This was determined by identifying the opioid measure value on the ROC curve with the shortest Euclidean distance to the upper-left corner of the ROC plot, representing the value closest to perfect discriminatory capability of 100% sensitivity and 100% specificity

These thresholds for the opioid prescription count and mean MME/day measures resulted in 19,166 and 23,122 subjects being flagged as high risk for an unintentional opioid overdose, respectively.

This represented roughly one-third of Aim 3 testing cohort subjects. The high number of people meeting these ROC model-derived thresholds presented a concern over excessive inclusiveness of these cutpoints in light of the fact that the NC MLIP was operating at administrative capacity two years into the program having enrolled a cumulative total of 4,400 beneficiaries. For this reason, alternative analyses of optimal opioid exposure measure cutpoints were performed by comparing log-likelihood values from a series of Cox proportional hazard models utilizing dichotomous opioid exposure indicator variables at varied cutpoints. (Despite not being further considered for validation, Cox model log likelihood plots for the pharmacy count and mean APAP mg/day measures are presented in Appendix Figures 4 and 5 for reference).

Five or more opioid prescription fills in a 60-day period was the optimal Cox model-derived cutpoint for predicting the primary outcome of an unintentional opioid overdose. This was determined because a cutpoint of five or more fills provided the best model fit based on its maximized log likelihood value (Figure 4.13). A cutpoint of three or more opioid fills performed best for all secondary outcomes, except for the unintentional acetaminophen overdose outcome, which had an optimal cutpoint of seven or more fills.

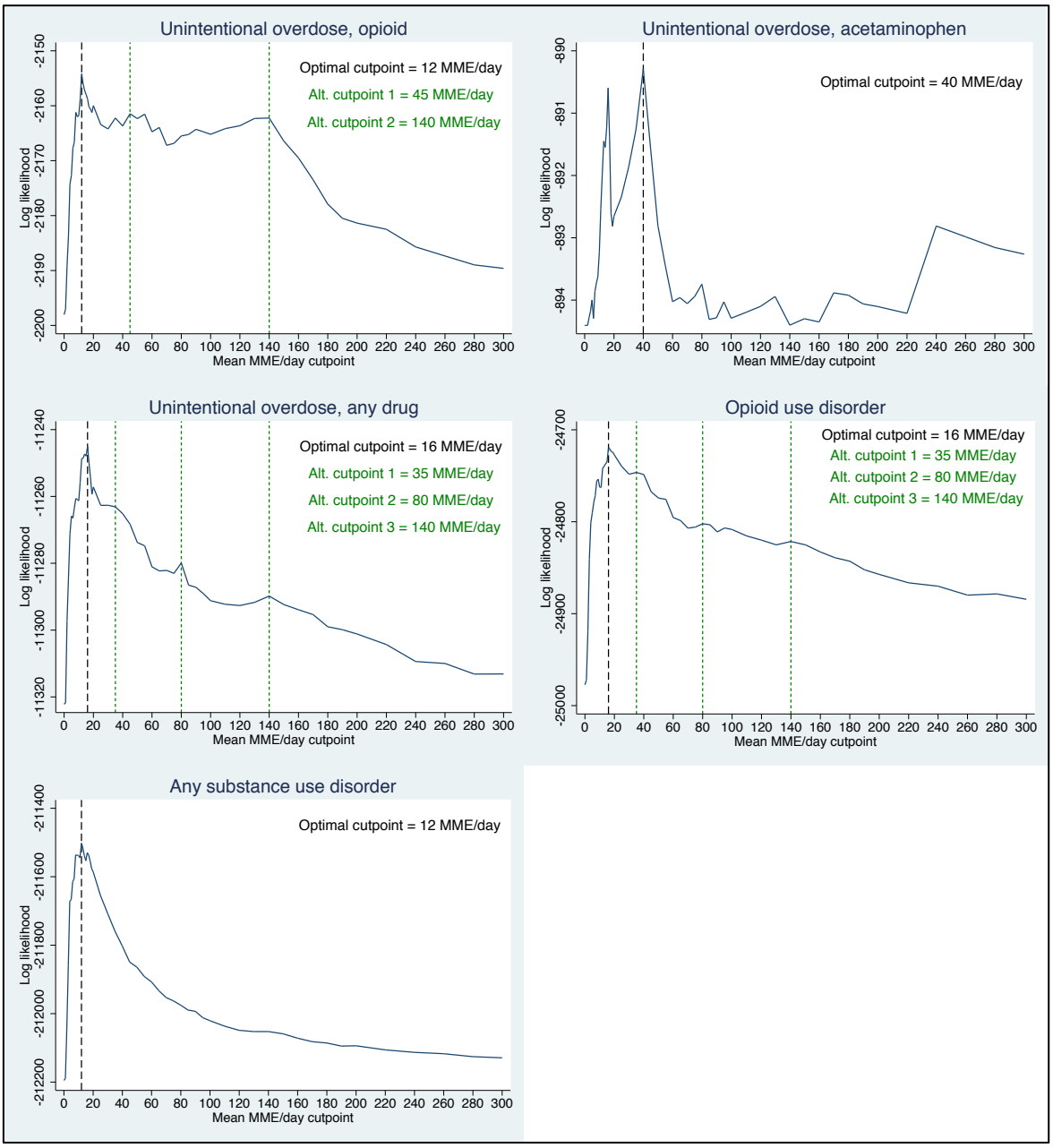
Figure 4.13: Distribution of log likelihood values from Cox proportional hazard models predicting Aim 3 outcomes at varied cutpoints of the opioid prescription fill count measure



The best performing Cox proportional hazard model for the exposure/outcome pairing of average MME/day and unintentional opioid overdose used a cutpoint of ≥12 MME/day (Figure 4.14). However, alternative cutpoints were identified at higher values of mean MME/day where additional peak log likelihood values were noted. Examination of log likelihood values at these higher MME/day values identified further cutpoints at ≥45 MME/day and ≥140 MME/day. These additional cutpoints were

obtained to provide high-performing, but less inclusive, MME/day threshold alternatives, because the optimal cutpoint of ≥12 MME/day flagged a high number of testing sample subjects (nearly one-third). Similar trends in optimal average MME/day cutpoints were observed in the Cox model series predicting secondary outcome events.

Figure 4.14: Distribution of log likelihood values from Cox proportional hazard models predicting Aim 3 outcomes at varied cutpoints of the mean MME/day measure



Note: MME=Milligram morphine equivalent

Results of the Aim 3 testing phase informed selection of opioid exposure measures and thresholds for performance evaluation in the validation sample. Based on findings from the survival ROC analyses, the opioid prescription fill count and average MME/day measures were selected for further examination as predictors of primary and secondary endpoints in the validation phase. Unique pharmacy counts and average APAP mg/day were deemed failures as discriminators of key clinical outcomes both individually and in combination with other opioid exposure measures. They were excluded from the validation phase. Optimal opioid fill count and mean MME/day cutpoints were informed by the results of the Cox model log likelihood distributions for each measure. The optimal threshold of opioid fill counts evaluated in the validation phase was ≥5 opioid fills in a 60-day period. The optimal threshold of mean MME/day evaluated in the validation phase was ≥12 MME/day in a 60-day period. Alternative MME/day cutpoints at ≥45 MME/day and ≥140 MME/day were also examined due to concerns over the ≥12 MME/day threshold's inclusiveness having limited utility in real-world MLIP applications.

4.3.3 Aim 3 Validation Phase Findings

For conciseness, validation phase results reported here focus on the performance of the selected opioid exposure measures and thresholds with regard to the primary outcome of unintentional opioid overdose. All analyses were performed for secondary clinical outcomes and are presented in full in relevant tables and figures in the Appendix, with in-text references to the Appendix provided.

Out of 69,667 validation sample subjects, 5,525 (7.9%) individuals received ≥5 opioid prescriptions in a 60-day period (Table 4.16). A total of 19,926 (28.6%); 7,541 (10.8%); and 1,980 (2.8%) subjects met the 60-day average daily opioid dose thresholds of ≥12 MME/day, ≥45 MME/day, and ≥140 MME/day, respectively. Unsurprisingly, the sensitivity of the measures in capturing unintentional opioid overdose events increased as the percentage of the cohort flagged by a criterion increased. The most inclusive measure—≥12 MME/day—resulted in the highest sensitivity, at 59%. In other words, 59% of subjects who had an accidental opioid overdose (in one person-year of time) were flagged as high-risk opioid users based on having ≥12 MME/day on average over a 60-day period. The least inclusive

individual criterion ≥140 MME/day, despite having the highest concentration of opioid overdose events for the number of people it flagged, was only 16% sensitive. Individual criterion selected from the testing phase generally exhibited high specificity of around 90% or greater. For example, with regard to the ≥5 opioid fill criterion, 92% of subjects who did not experience an unintentional opioid overdose event were correctly classified as not high risk. The ≥12 MME/day criterion exhibited the lowest specificity at 72%. By point of comparison, the currently employed NC MLIP criteria of ≥7 opioid fills in a two-month period flagged the fewest subjects as high risk (2.4%), had the lowest sensitivity for accidental opioid overdose (9%), and had the highest specificity (98%).

Table 4.16: Describing application of selected opioid use criteria in Aim 3 validation sample for primary unintentional opioid overdose outcome

	Criterion met (N=69,667)		**Experienced outcome event* (N=174)**			
	n	(% of total cohort)	n	(% within criterion)	**Sens.** Ŧ	**Spec.** Ŧ
Individual measures						
≥5 opioid fills	5525	(7.9%)	47	(0.9%)	0.255	0.921
≥12 MME/day	19926	(28.6%)	112	(0.6%)	0.592	0.715
≥45 MME/day	7541	(10.8%)	66	(0.9%)	0.329	0.892
≥140 MME/day	1980	(2.8%)	33	(1.7%)	0.159	0.972
NC MLIP standard: ≥7 opioid fills	1703	(2.4%)	16	(0.9%)	0.087	0.976
Combined criteria (unconditional)						
≥5 opioid fills or ≥12 MME/day	20404	(29.3%)	115	(0.6%)	0.608	0.708
≥5 opioid fills or ≥45 MME/day	10545	(15.1%)	80	(0.8%)	0.415	0.850
≥5 opioid fills or ≥140 MME/day	6336	(9.1%)	62	(1.0%)	0.330	0.910
≥7 opioid fills or ≥12 MME/day	19970	(28.7%)	112	(0.6%)	0.592	0.714
≥7 opioid fills or ≥45 MME/day	8370	(12.0%)	68	(0.8%)	0.343	0.881
≥7 opioid fills or ≥140 MME/day	3336	(4.8%)	42	(1.3%)	0.214	0.953
Combined measures (conditional)						
≥5 opioid fills and ≥12 MME/day	5047	(7.2%)	44	(0.9%)	0.238	0.928
≥5 opioid fills and ≥45 MME/day	2521	(3.6%)	33	(1.3%)	0.166	0.964
≥5 opioid fills and ≥140 MME/day	1169	(1.7%)	18	(1.5%)	0.087	0.983
≥7 opioid fills and ≥12 MME/day	1659	(2.4%)	16	(1.0%)	0.087	0.976
≥7 opioid fills and ≥45 MME/day	874	(1.3%)	14	(1.6%)	0.072	0.988
≥7 opioid fills and ≥140 MME/day	347	(0.5%)	7	(2.0%)	0.034	0.995

Note: Sens=Sensitivity; Spec=Specificity; MME=Milligram morphine equivalent; NC MLIP=North Carolina Medicaid lock-in program.
*Reported percentages in the "Experienced outcome event" column refer to the proportion of subjects flagged as high risk for that given opioid use criterion in that row.
Ŧ Reported sensitivities and specificities are time-dependent measures calculated at 365 days of follow-up using survival ROC models accounting for time to event. Interpretation of these figures should be per-person-year.

Unconditional combinations of the ≥5 opioid fill criteria with each of the three MME/day criteria resulted in marginal increases in sensitivity and decreases in specificity in comparison to individual measure performance. However, conditional combinations of these measures—in which subjects were required to satisfy both opioid thresholds in the combination—greatly reduced the number of subjects flagged as high risk, decreased criteria sensitivity, and increased its specificity. For example, 2,521 subjects received ≥5 opioid fills and had an average daily opioid dose of ≥45 MME/day, while these measures would have individually flagged 5,525 and 7,541 subjects as high risk, respectively. The conditional combination of these criteria also resulted in a similar decrease in sensitivity for capturing the unintentional opioid overdose outcome, from 26-33% sensitivity individually to 17% sensitivity when combined in this way. However, the criteria of ≥5 opioid fills and ≥45 MME/day resulted in 96% specificity. Descriptive statistics for combinations of the NC MLIP current criterion of ≥7 fills with the mean MME/day measures, as expected, was more restrictive than the ≥5 fill, less sensitive, and more specific than the ≥5 opioid fill combinations.

The optimal thresholds of the opioid fill count measure and average daily opioid dose measures were less sensitive in capturing secondary outcome measures than they were for the primary unintentional opioid overdose outcome (Appendix Tables 30-33). For example, the ≥45 MME/day criterion was 33% sensitive for the primary outcome, but it was only 18%, 20%, 25%, and 15% sensitive for the unintentional APAP overdose, any overdose event, opioid use disorder, and any substance use disorder secondary outcomes, respectively.

Each opioid use measure criterion, both individually and in combination, were highly predictive of the primary outcome of unintentional opioid overdose in Cox proportional hazard modeling (Table 4.17). In general, the hazard of an accidental opioid overdose was 4 to 7 times higher for subjects meeting a criterion for high risk opioid use, compared to subjects whose opioid use was below that threshold. Log likelihood values from each Cox model, which indicate model fit, show that a criterion's performance in predicting an unintentional opioid overdose increased as the criterion's inclusiveness increased. However, all three mean MME/day criteria had higher log likelihood values than the opioid prescription count

measures. This held true even for the ≥140 MME/day criterion, which flagged roughly one-third the number of subjects identified by the ≥5 opioid fill criterion as high risk.

Table 4.17: Bivariate Cox proportional hazard model results estimating the hazard of an unintentional opioid overdose for each opioid use criterion

	Criterion met (N=69,667)			
	n (%)	**Hazard ratio**	**95% CI**	**LL**
Individual measures				
≥5 opioid fills	5525 (7.9%)	4.09	(2.93 , 5.72)	-1864.2
≥12 MME/day	19926 (28.6%)	3.99	(2.93 , 5.44)	-1850.3
≥45 MME/day	7541 (10.8%)	4.36	(3.21 , 5.92)	-1853.8
≥140 MME/day	1980 (2.8%)	6.88	(4.71 , 10.05)	-1857.9
NC MLIP standard: ≥7 opioid fills	1703 (2.4%)	3.82	(2.28 , 6.39)	-1881.5
Combined criteria (unconditional)				
≥5 opioid fills or ≥12 MME/day	20404 (29.3%)	4.18	(3.05 , 5.72)	-1847.9
≥5 opioid fills or ≥45 MME/day	10545 (15.1%)	4.29	(3.19 , 5.78)	-1849.9
≥5 opioid fills or ≥140 MME/day	6336 (9.1%)	5.19	(3.80 , 7.07)	-1847.7
≥7 opioid fills or ≥12 MME/day	19970 (28.7%)	3.98	(2.92 , 5.43)	-1850.5
≥7 opioid fills or ≥45 MME/day	8370 (12.0%)	4.12	(3.04 , 5.58)	-1855.5
≥7 opioid fills or ≥140 MME/day	3336 (4.8%)	5.69	(4.02 , 8.06)	-1856.3
Combined measures (conditional)				
≥5 opioid fills and ≥12 MME/day	5047 (7.2%)	4.09	(2.91 , 5.76)	-1865.6
≥5 opioid fills and ≥45 MME/day	2521 (3.6%)	5.55	(3.80 , 8.11)	-1863.6
≥5 opioid fills and ≥140 MME/day	1169 (1.7%)	5.85	(3.59 , 9.52)	-1874.5
≥7 opioid fills and ≥12 MME/day	1659 (2.4%)	3.91	(2.34 , 6.54)	-1881.2
≥7 opioid fills and ≥45 MME/day	874 (1.3%)	6.14	(3.56 , 10.60)	-1877.4
≥7 opioid fills and ≥140 MME/day	347 (0.5%)	7.17	(3.37 , 15.28)	-1883.1

Note: CI=Confidence interval; LL=Log likelihood; MME=Milligram morphine equivalent; NC MLIP=North Carolina Medicaid lock-in program. All hazard ratio estimates reported in this table were statistically significant at $p<0.001$.

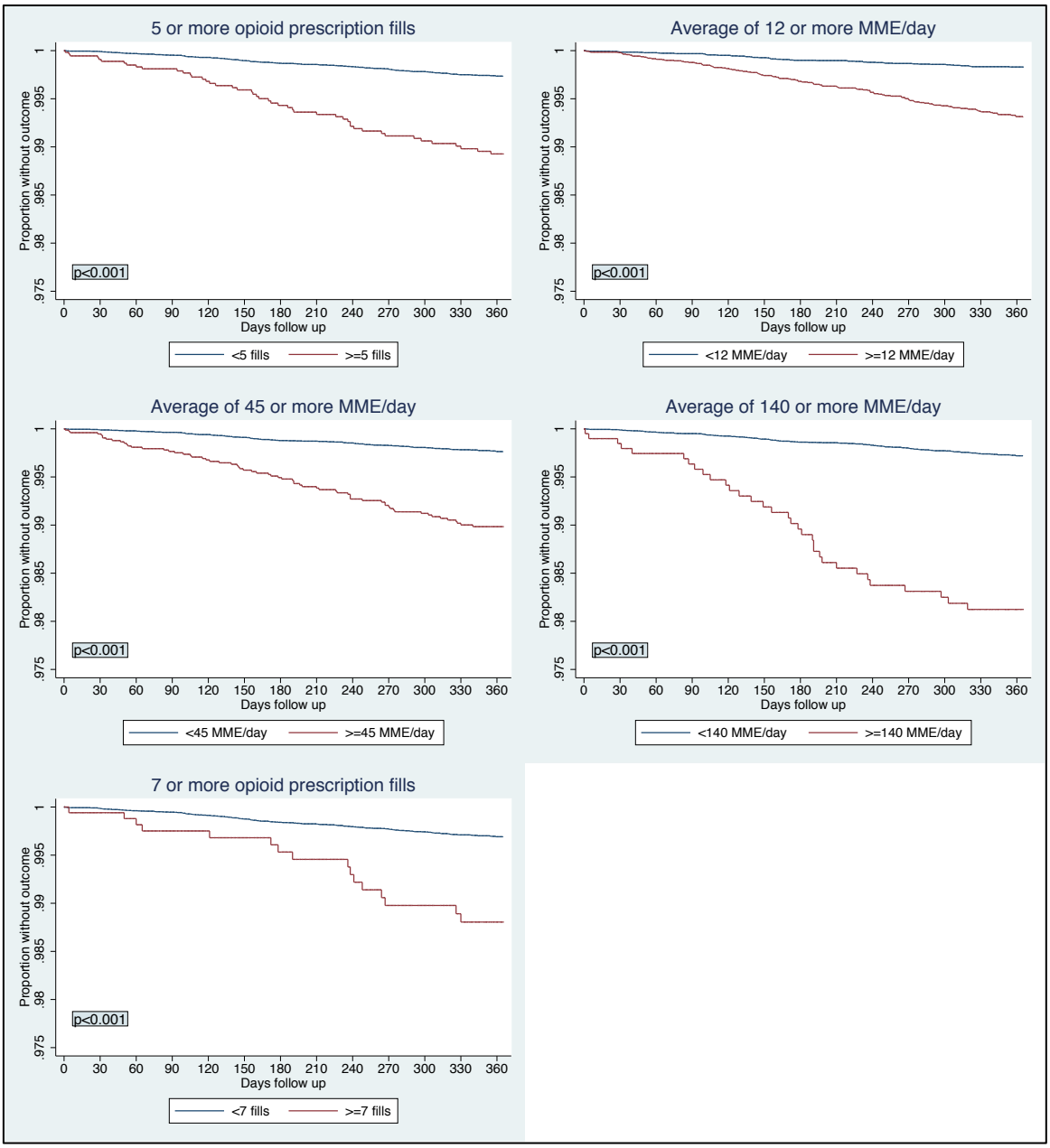
All unconditional combinations of ≥5 opioid fills and the MME/day thresholds performed similarly and were better predictors of unintentional opioid overdose than any of the individual criteria.

The conditional combinations of opioid use criteria, which were more restrictive, had lower log likelihood values than the unconditional combinations and the individual mean MME/day measures but performed similarly to the ≥5 opioid fill individual criterion. The NC MLIP standard eligibility measure of ≥7 opioid fills, both alone and in combination, was significantly predictive of the primary outcome but did not outperform the other measures, in terms of Cox model log likelihood.

Aside from the unintentional APAP overdose, each opioid use criterion measure was also highly predictive of the secondary outcomes (Appendix Tables 34-37). However, the magnitude of the hazard ratio point estimates for secondary outcomes were roughly half those observed when estimating the primary outcome. The secondary outcome model performance trends across opioid use measures were similar to those observed in models estimating the primary outcome. In general, the average MME/day criteria were more predictive of the secondary outcomes—particularly the ≥12 MME/day and ≥45 MME/day cutpoints—compared to the opioid fill count measures.

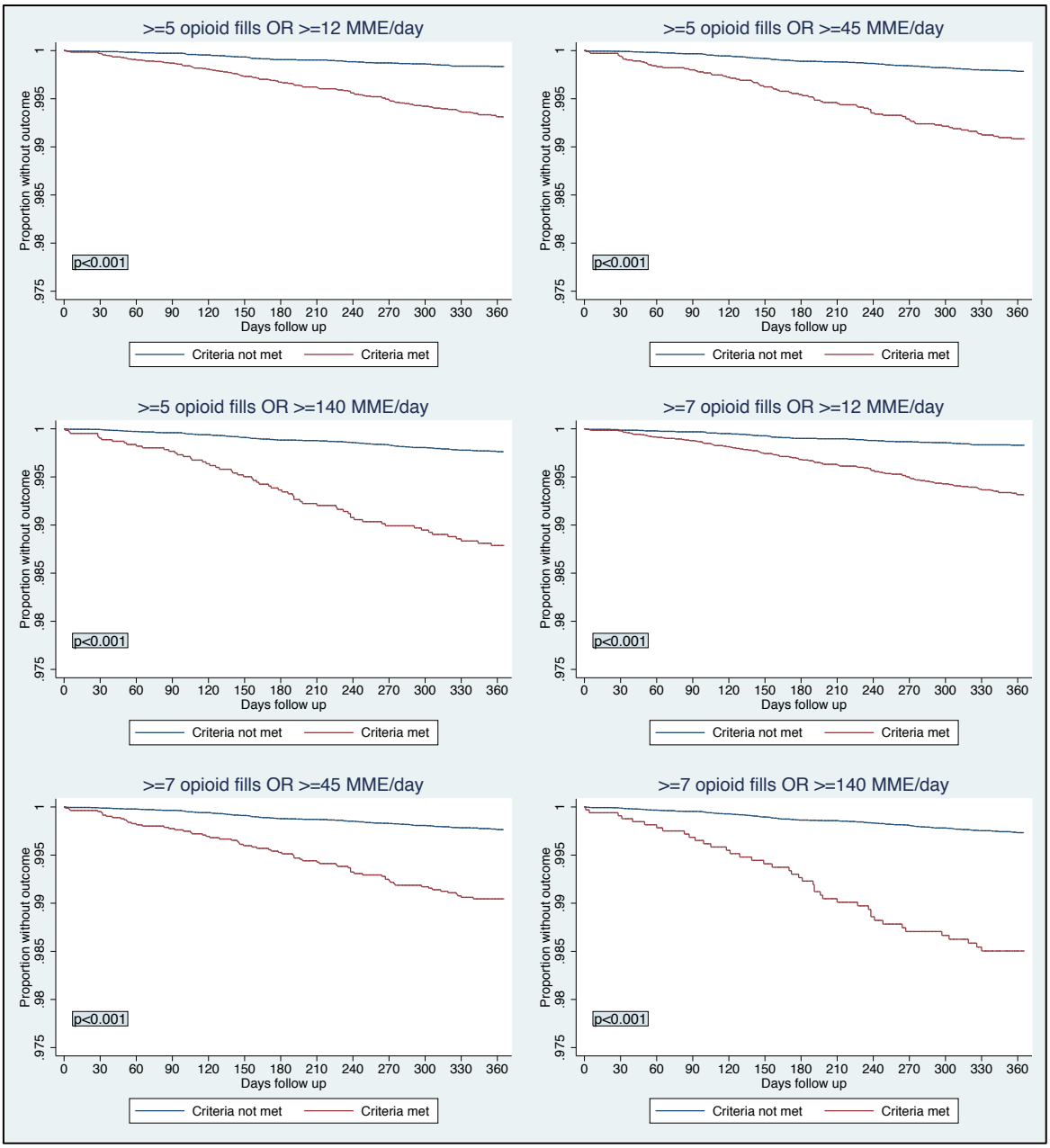
Kaplan-Meier survival function analyses were the final method employed to assess the performance of opioid use measures and thresholds identified from the testing phase in predicting relevant public health outcomes from high risk opioid use. All Kaplan-Meier survival function models showed a statistically significant decrease in likelihood of not experiencing an unintentional opioid overdose over time ($p<0.001$ for all) (Figures 4.15-4.17). In other words, the probability of experiencing the primary outcome was significantly higher over time among subjects who met each criterion for high-risk opioid use. Visual inspection of the Kaplan-Meier plots showed that the criterion of ≥140 MME/day, alone and in combination, consistently produced the greatest disparity in risk of an unintentional opioid overdose between those meeting and those not meeting the criterion. Similar findings were observed for the secondary outcomes (Appendix Figures 6-17), except for the unintentional APAP overdose outcome for which the predictive performance of the opioid use measures was much less pronounced or nonexistent.

Figure 4.15: Kaplan-Meier survival function plots of time to an unintentional opioid overdose event, by individual high risk opioid use measure criteria



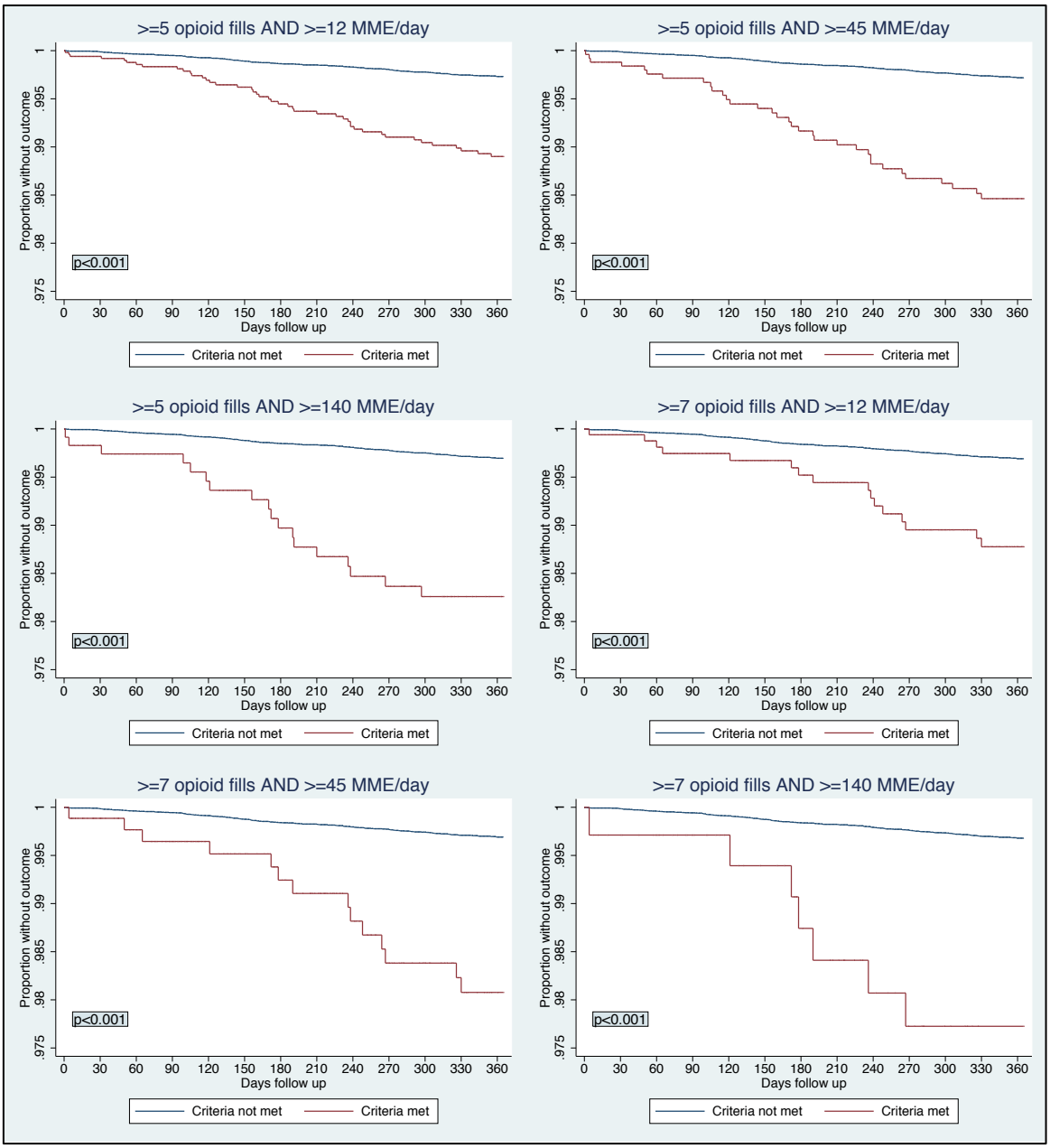
Note: p-values refer to the statistical test for the hypothesis that the survivor functions are equal

Figure 4.16: Kaplan-Meier survival function plots of time to an unintentional opioid overdose event, by unconditional combination of high risk opioid use measure criteria



Note: p-values refer to a statistical test for the hypothesis that the survivor functions are equal

Figure 4.17: Kaplan-Meier survival function plots of time to an unintentional opioid overdose event, by conditional combination of high risk opioid use measure criteria



Note: p-values refer to a statistical test for the hypothesis that the survivor functions are equal

Kaplan-Meier model estimates of unintentional opioid overdose risk over time were also used to examine differences in absolute risk of the primary outcome between subjects meeting a given opioid use measure threshold and those below the threshold (Table 4.18). Although the risk of an unintentional opioid overdose was significantly higher among subjects meeting a given opioid use measure criterion,

the absolute risk difference was small (typically <1%). This is largely due to the primary outcome being uncommon in the sample, occurring in 0.25% of the validation sample subjects. However, using the absolute risk difference to calculate the number needed to enroll (NNE) provided a more intuitive interpretation of how these opioid use criteria performed in practice.

Table 4.18: Kaplan-Meier estimates of unintentional opioid overdose event, by opioid use criterion, represented as absolute risk differences and numbers needed to enroll

	Criterion met (N=69,667)	Follow-up time							
		30 days		90 days		180 days		365 days	
	n (%)	ARD	NNE	ARD	NNE	ARD	NNE	ARD	NNE
Individual measures									
≥5 opioid fills	5525 (7.9%)	0.0008	1215	0.0014	703	0.0044	228	0.0081	124
≥12 MME/day	19926 (28.6%)	0.0001	18197	0.0009	1094	0.0022	456	0.0052	192
≥45 MME/day	7541 (10.8%)	0.0004	2400	0.0020	503	0.0038	260	0.0078	129
≥140 MME/day	1980 (2.8%)	0.0014	712	0.0032	317	0.0090	111	0.0159	63
NC MLIP standard: ≥7 opioid fills	1703 (2.4%)	0.0004	2293	0.0019	513	0.0031	323	0.0088	113
Combined measures (unconditional)									
≥5 opioid fills or ≥12 MME/day	20404 (29.3%)	0.0002	5134	0.0010	971	0.0023	427	0.0053	189
≥5 opioid fills or ≥45 MME/day	10545 (15.1%)	0.0005	2034	0.0017	599	0.0035	289	0.0070	143
≥5 opioid fills or ≥140 MME/day	6336 (9.1%)	0.0009	1132	0.0019	518	0.0052	193	0.0097	103
≥7 opioid fills or ≥12 MME/day	19970 (28.7%)	0.0001	18376	0.0009	1097	0.0022	458	0.0052	192
≥7 opioid fills or ≥45 MME/day	8370 (12.0%)	0.0004	2759	0.0019	526	0.0035	285	0.0072	139
≥7 opioid fills or ≥140 MME/day	3336 (4.8%)	0.0008	1277	0.0027	371	0.0060	167	0.0123	81
Combined measures (conditional)									
≥5 opioid fills and ≥12 MME/day	5047 (7.2%)	0.0005	2142	0.0012	863	0.0042	239	0.0083	121
≥5 opioid fills and ≥45 MME/day	2521 (3.6%)	0.0011	937	0.0024	425	0.0070	144	0.0125	80
≥5 opioid fills and ≥140 MME/day	1169 (1.7%)	0.0016	634	0.0020	491	0.0088	114	0.0143	70
≥7 opioid fills and ≥12 MME/day	1659 (2.4%)	0.0005	2212	0.0020	497	0.0032	312	0.0091	110
≥7 opioid fills and ≥45 MME/day	874 (1.3%)	0.0010	1006	0.0030	334	0.0060	167	0.0161	62
≥7 opioid fills and ≥140 MME/day	347 (0.5%)	0.0027	366	0.0023	434	0.0110	91	0.0195	51

Note: ARD=Absolute risk difference; NNE=Number needed to enroll; MME=Milligram morphine equivalent; NC MLIP=North Carolina Medicaid lock-in program. ARD was calculated from Kaplan-Meier survival function models by subtracting the probability of experiencing the outcome event at a given time point among those below an opioid use measure threshold from the probability of experiencing the outcome event at that same time among those meeting the threshold. The NNE was calculated as (1 / ARD) and is interpreted as the number of individuals needed to enroll into a hypothetical MLIP program based on a given opioid use criterion in order to have the opportunity to prevent one outcome event.

Based on these findings, a hypothetical MLIP program that used an eligibility criterion of ≥5 opioid prescription fills in a 60-day period would need to enroll 124 opioid users based on this criterion in

order to the have opportunity to prevent one unintentional opioid overdose event. The NNE values for the individual ≥12 MME/day, ≥45 MME/day, and ≥140 MME/day at 365 days of follow-up for the primary outcome were 192, 129, and 63, respectively. An opioid use measure's NNE generally decreased as the proportion of the validation sample flagged as high risk based on that measure decreased. However, the current NC MLIP criteria of ≥7 opioid fills had nearly twice the NNE as the ≥140 MME/day measure, despite flagging roughly the same number of subjects as high risk.

Because the absolute risk difference and NNE are a function of underlying prevalence of the outcome, NNEs for the rare secondary outcome of unintentional acetaminophen overdose were substantially higher than the primary outcome, while NNEs were lower for the other three secondary outcomes that were more prevalent than the primary outcome (Appendix Tables 38-41). The NNEs of the individual exposure measures for the primary outcome ranged from 63 (≥140 MME/day) to 192 (≥12 MME/day). The NNE ranges for the unintentional acetaminophen overdose, any drug overdose, opioid use disorder diagnosis, and any substance use disorder diagnosis secondary outcomes were 275-909, 31-56, 10-25, and 4-7, respectively.

CHAPTER V: DISCUSSION

5.1 DISSERTATION OBJECTIVES RECAP

This dissertation comprised three retrospective cohort studies investigating the North Carolina Medicaid Recipient Management Lock-in Program through use of administrative Medicaid claims data and data from the state's PDMP. The NC MLIP is one of at least 46 controlled substance lock-in programs operated by state Medicaid programs across the country.[147] MLIPs attempt to reduce high-risk controlled substance use behaviors by identifying beneficiaries with high utilization of controlled substance medication services and restricting their access to a small number of designated providers for Medicaid coverage of these services—typically one prescriber and one pharmacy. Despite their high prevalence, there exists little rigorous evidence to inform the optimal design of MLIPs and to substantiate their effectiveness in achieving their stated public health aims of reducing high-risk and nonmedical use of controlled substance medications through enhanced care coordination.

The purpose of this dissertation was to provide what is believed to be among the first examinations of known limitations to the MLIP policy strategy. The first MLIP limitation of interest was the problem of lock-in circumvention. MLIP circumvention occurs when enrollees obtain controlled substance medications from non-lock-in providers by paying for them entirely out-of-pocket. MLIP circumvention is currently unobservable and unenforceable by MLIP administrators and results in a breach in the MLIP's enhanced care coordination for these high-risk individuals. The second MLIP limitation of interest was the lack of literature to support development of MLIP eligibility criteria that identify Medicaid beneficiaries at highest risk for adverse clinical outcomes from prescription drug abuse.

Aim 1 of this dissertation utilized a longitudinal retrospective cohort of NC MLIP enrollees to assess the prevalence of controlled substance circumvention in this population and to isolate the effect of MLIP enrollment, as well as patient-level predictors, on the likelihood and extent of engaging in MLIP

circumvention behavior. Aim 2 built on this study by investigating MLIP circumvention patterns at the prescription level. Aim 2 examined the effect of NC MLIP enrollment, as well as patient-level predictors, on three prescription-level outcomes indicative of their risk and abuse potential within the context of circumvented and Medicaid-covered behaviors. Aim 3 employed predictive modeling techniques to test and validate claims-based measures of high-risk opioid use that were most predictive of overdose events and substance use disorders in an NC Medicaid population.

5.2 SUMMARY OF FINDINGS

5.2.1 Summary of Findings—Aim 1

Out of over 4,400 NC Medicaid beneficiaries who were enrolled in the NC MLIP during its first two years of operation, a total of 1,647 MLIP enrollees were included in Aim 1 analyses. This cohort was about 40 years of age, on average, and mostly female, White, and residents of metropolitan counties in NC. Nearly all subjects had a baseline diagnosis of chronic noncancer pain and there was high mental health and physical comorbid burden in the cohort. High opioid utilization was the primary cause of MLIP eligibility for these subjects. Nearly all subjects experienced an MLIP enrollment delay. On average, the Aim 1 cohort was not subject to the MLIP intervention until nearly six months after first demonstrating high risk controlled substance use, as defined by the NC MLIP eligibility criteria.

All findings from Aim 1 descriptive, bivariate, and GEE modeling analyses clearly indicated that enrollment in the NC MLIP induced subjects to engage in controlled substance circumvention behavior. The mean number of circumvented opioids and benzodiazepine prescriptions per-person-per-month tripled following MLIP enrollment. When adjusting for policy- and patient-level characteristics, enrollment in the NC MLIP was associated with 3.6 times higher likelihood of engaging in circumvention in a given month. MLIP enrollment also had similar effects on increases in the extent of circumvention behavior within a given person-month.

The marked increase in circumvention behavior following MLIP enrollment substantially offset what appeared, from NC Medicaid's perspective, to be a drastic reduction in controlled substance use attributed to the MLIP. Looking only at NC Medicaid claims data—which would be the only data source

available to NC MLIP administrators to evaluate program outcomes—Medicaid prescription claims for opioids and benzodiazepines dropped over 40% after subjects were enrolled in the MLIP, from 2.72 claims per-person-per-month to 1.39 claims. However, what NC Medicaid could not observe was that over half of this decrease in Medicaid claims for controlled substances was offset by an increase in controlled substance prescription fills obtained through circumvention.

Aside from MLIP enrollment, GEE models from Aim 1 revealed additional factors associated with increased controlled substance circumvention behavior. The likelihood and extent of circumvention increased roughly 25% during periods in which subjects had demonstrated high-risk controlled substance use qualifying them for the MLIP but had not yet been enrolled in the program. Additionally, subjects who qualified for the MLIP due to high utilization of benzodiazepines and pharmacies were more likely to circumvent. Numerous patient-level characteristics were also associated with circumvention. This behavior was more common among MLIP enrollees who were younger, living in areas with high supplies of dispensing pharmacies, had anxiety disorder diagnoses, and had a high physical comorbidity burden.

5.2.2 Summary of Findings—Aim 2

A total of 98,243 opioid analgesic prescription fills from 1,646 NC MLIP enrollees were included in Aim 2 analyses. Overall, 80% of the prescriptions were paid for using Medicaid coverage, while the remaining 20% were obtained through circumvention. Sixty-one percent of opioid prescriptions contained Schedule II products, 18% contained a long acting opioid formulation, and the mean prescribed daily opioid dose was 79 MME/day.

Short acting oral hydrocodone (Vicodin, Norco) and oxycodone (Percocet, Roxicodone) were by far the most common opioid products received by subjects through circumvention and Medicaid coverage. There were few notable changes in opioid product prevalence before and after MLIP enrollment to suggest obvious targeting of specific opioid products for circumvention. The prevalence of long acting oxycodone (Oxycontin) among circumvented prescriptions decreased by half after MLIP enrollment. However, this finding may have been an artifact of underlying changes in prescribing practices in which long acting oxymorphone (Opana ER) gained market share as an alternative to long

acting oxycodone.[253] Of note, though, methadone was the most commonly circumvented long acting opioid product and in the top three of most commonly circumvented Schedule II opioid products. However, among Medicaid covered prescriptions, methadone was only the fifth most common long acting opioid and not even among the top five most common Schedule II products.

The risk profile of opioid prescriptions—characterized by the proportion of prescriptions written for Schedule II and long acting opioid products and the mean prescribed MME/day—was comparable between circumvented and Medicaid-paid opioid fills before MLIP enrollment. After MLIP enrollment, however, opioid prescriptions paid for using NC Medicaid coverage contained Schedule II opioids 30% more often, long acting opioids twice as often, and had nearly 50% higher average daily doses of opioids. Opioid prescriptions obtained through circumvention did not experience any increase in prescription-level risk measures. The proportion of long-acting opioid fills and average daily opioid dose actually decreased after MLIP enrollment in the context of circumvention behavior.

These trends were confirmed in GLM analysis adjusting for policy- and patient-level characteristics. MLIP enrollment had no association with the likelihood of circumventing Schedule II opioid products or on the average MME/day of circumvented opioid prescriptions. The likelihood of circumventing a long acting opioid decreased 42% following MLIP enrollment. Opioid prescriptions paid by subjects using their Medicaid coverage were 30% more likely to contain a Schedule II opioid, twice as likely to be written for a long-acting opioid formulation, and had an additional 55 MME prescribed/day compared to Medicaid covered opioid prescriptions prior to MLIP enrollment.

Although MLIP enrollment was not associated with an increase in risk profile of opioid prescriptions obtained through circumvention, GLM models identified a handful of patient-level characteristics associated with increased likelihood of circumventing an opioid prescription with a high-risk attribute: male sex, residence in a border county, depression, and high physical comorbidity burden.

5.2.3 Summary of Findings—Aim 3

Nearly 140,000 adult NC Medicaid beneficiaries were included in Aim 3 analysis investigating the performance of potential MLIP eligibility criteria as they are currently applied in the NC MLIP. Half

of subjects were used to test opioid exposure measures, and the other half were used to validate optimal measures and thresholds identified in the testing phase. The primary outcome of interest was unintentional opioid overdose, for which 376 subjects recorded the primary outcome. Secondary outcomes were unintentional APAP overdose, an unintentional overdose of any drug, opioid use disorder diagnosis, and any substance use disorder diagnosis.

Based on survival ROC analysis, no single opioid exposure measure, or combination thereof, even reached "fair" discriminatory performance in predicting subjects who experienced a study outcome versus those that did not. Measures of number of unique pharmacies used to obtain opioids and average daily APAP dosage from opioid/APAP combination products failed as predictors and were excluded from further evaluation. Measures of number of opioid prescription fills and average MME/day over a 60-day period were on the high end of the "poor" performance with AUCs of 0.67 and 0.68 for the primary outcome, respectively. These two measures were further validated using optimal thresholds of ≥5 opioid prescription fills and ≥12 MME/day (with alternative high-performing cutpoints at ≥45 MME/day and ≥140 MME/day).

Overall, sensitivity was low for capturing subjects with the primary outcome event using the best performing opioid exposure criteria identified in the testing phase. The ≥12 MME/day criterion was 59% sensitive, while the alternative mean MME/day cutpoints and the ≥5 opioid fill measure were 16-33% sensitive. Specificity of these measures was generally over 90%, except for the ≥12 MME/day criterion which was 72% specific for the primary outcome. Despite low sensitivity, the opioid use criteria selected for validation were all highly predictive of the study outcomes in bivariate Cox proportional hazard modeling. Subjects flagged as high risk based on these measures had 4 to 7-times higher hazard of an unintentional opioid overdose compared to those classified as low-risk for that measure. Based on bivariate Kaplan-Meier survival models, an MLIP would need to enroll 124, 192, 129, and 63 subjects based on thresholds of ≥5 opioid fills, ≥12 MME/day, ≥45 MME/day, and ≥140 MME/day over 60 days, respectively, to have the opportunity to prevent one accidental opioid overdose. Improved criterion performance across all evaluative methods was largely dictated by a positive relationship with the number

of subjects flagged as high risk. The current NC MLIP eligibility criterion of ≥7 opioid fills performed demonstrably worse than the optimal opioid use measures selected in Aim 3.

5.3 POLICY IMPLICATIONS

Many stakeholders have tapped MLIPs as a policy tool worthy of serious consideration in forthcoming national efforts to mitigate prescription drug abuse behaviors.[23,24,130] A bill was even introduced in the United States House of Representatives Ways and Means Committee in December 2014 recommending establishment of a controlled substance lock-in program in Medicare to prevent fraud, waste, and abuse of prescription drugs in the Medicare population.[254] It is understandable why momentum exists behind proliferation of MLIP-type interventions. The national epidemic of prescription drug abuse has garnered well-deserved attention as a public health crisis requiring, according to CDC director Thomas Frieden, an "all-hands-on-deck approach" to correcting it.[255] State Medicaid agencies often justify the existence of their MLIPs primarily as a tool for improving public health among patients at greatest risk for adverse substance use outcomes.[256] However, the available evidence to support the effectiveness of MLIPs in achieving desired public health outcomes around prescription drug abuse is scant. This dissertation served to reinforce the current lack of understanding about the effectiveness and optimal design of MLIPs. Our findings from an evaluation of the NC MLIP elucidated key limitations of current MLIP operations that must be further examined and reconciled to achieve the optimal public health benefit of the MLIP policy strategy moving forward.

5.3.1 Policy Implications—MLIP Enrollment Delays

The initial purpose of this dissertation was to investigate MLIP circumvention behaviors and the performance of MLIP eligibility criteria. However, an additional challenge facing MLIP effectiveness was uncovered in the process of conducting Aims 1 and 2—the MLIP enrollment delay. Roughly 95% of the over 1,600 NC MLIP enrollees analyzed in Aims 1 and 2 experienced a delay in MLIP enrollment of nearly six months, on average, from the time they first became eligible for the program. This meant that nearly all NC MLIP enrollees didn't experience the policy intervention until half a year after they exhibited high-risk controlled substance use behavior. Although much work is needed to establish

whether and to what extent MLIPs reduce adverse substance use and overdose outcomes, MLIPs are incapable of preventing these outcomes if patients are not enrolled in the MLIP until months after they were determined to be in need of this intervention. In the Aim 3 validation sample, 57% of unintentional opioid overdose events occurred less than 180 days from being flagged as high-risk using a measure of ≥5 opioid fills in a 60-day period. A MLIP with a six-month enrollment delay would have missed the opportunity to prevent these overdoses. Bolstering MLIP effectiveness will require minimizing the time between beneficiaries exhibiting high-risk prescription drug use behaviors and enrollment in the MLIP. This will likely require enhancing resources dedicated to MLIP administration, as enrollment delays appear to primarily be a symptom of inadequate funding and human capital required to keep up with the administratively intensive tasks of identifying, notifying, and enrolling MLIP-eligible patients.

5.3.2 Policy Implications—MLIP Circumvention

Aims 1 and 2 provided among the first pieces of rigorous evidence that MLIP circumvention behavior undermines the policy's intended outcomes. Prior MLIP evaluations in the published and grey literature measured the effect of MLIP enrollment on controlled substance utilization from Medicaid's perspective—solely using Medicaid claims data. In Aim 1, we observed a 43% reduction in Medicaid claims for opioids and benzodiazepines following MLIP enrollment. This finding is in line with those reported by previous MLIP evaluations.[117-119] However, what prior evidence has failed to capture is the extent of controlled substance use taking place outside the scope of the Medicaid program. We found that over half of the observed reduction in controlled substance Medicaid prescription claims was offset by an increase in circumvented controlled substance prescriptions stemming from NC MLIP enrollment.

It is clear from Aim 1 that imposing prescriber and pharmacy access restrictions on NC MLIP enrollees caused these high risk patients to more frequently pay for controlled substance prescriptions entirely out-of-pocket, obviating the underlying purpose of the policy intervention. It is impossible to assess patient motivation behind this circumvention behavior given the limitations of the study data, but it likely falls into one of three categories: 1) circumvention to facilitate continued controlled substance abuse and/or diversion activities, 2) circumvention as a means to obtain necessary controlled substance

therapies in the face of new unintended access barriers caused by MLIP restrictions, or 3) circumvention to avoid heightened surveillance of their healthcare use behaviors by Medicaid authorities, even for necessary care. Regardless of the circumstances motivating individuals to circumvent Medicaid to obtain controlled substances, circumvention behavior poses a non-ignorable threat to MLIP effectiveness.

MLIP circumvention fails to prevent access to controlled substance prescriptions among enrollees intent on procuring them for abuse or diversion. We have shown that it is feasible and common for high-risk MLIP enrollees to, in the face of MLIP restrictions, readily obtain prescription medications implicated in the vast majority of preventable prescription drug overdose events in the US entirely unbeknownst to Medicaid. MLIP circumvention among program enrollees with legitimate medical need for opioids and benzodiazepines may be a symptom of unintended barriers to necessary care caused by MLIP enrollment. For example, a hypothetical MLIP enrollee may have been forced to pay cash for a necessary prescription fill of short-acting opioids to treat legitimate breakthrough pain if they were not located within a reasonable distance to their lock-in pharmacy at the time of need. In this scenario, MLIP-induced circumvention introduces unintended fragmentation in healthcare delivery for high-risk patients with legitimate medical need for opioids and benzodiazepines. In addition, MLIP circumvention to obtain necessary treatments imposes unnecessary added financial burden on patients with pre-existing financial vulnerability. Further research is needed to determine the actual root causes of MLIP circumvention, but in any scenario, MLIP circumvention results in a failure to maintain the enhanced care coordination between MLIP enrollees and their lock-in providers, which is purported to be the primary mechanism for achieving MLIPs' potential public health benefit.[147]

Aim 2 findings did identify one silver lining to the issue of the MLIP circumvention. Although MLIP enrollment caused subjects to circumvent more often, this additional circumvention behavior was not any riskier at the prescription-level. The likelihood of a circumvented opioid prescription being written for a Schedule II product was not significantly different after MLIP enrollment. The likelihood of a circumvention opioid prescription containing a long-acting opioid product decreased and the prescribed average daily opioid of circumvented opioid prescriptions decreased after MLIP enrollment. All three of

these outcomes reflected an individual prescription's risk for contributing to adverse substance use and overdose outcomes. The highest risk prescriptions—those containing Schedule II opioids, long acting opioid formulations, and high daily doses—were more heavily concentrated within the Medicaid program after MLIP enrollment. It is possible this trend was driven by cost, in which the high cost of certain common Schedule II, long acting, and high dose products, like fentanyl transdermal patches, were too cost prohibitive for MLIP enrollees to purchase out of pocket. Regardless, the MLIP's effect on reducing prescription drug abuse outcomes is aided by the fact that the highest risk prescriptions were obtained under the purview of a subject's MLIP providers after MLIP enrollment.

However, Aim 2 did indicate a troubling MLIP circumvention trend. Methadone prescriptions were among the most commonly circumvented medications both at baseline and after MLIP enrollment. Prior literature has shown methadone to be one of the most, if not the most, dangerous prescription opioid analgesic in terms of contributing to overdose events.[72,209] In North Carolina in 2007, methadone was responsible for over 1/3 of all poisoning deaths in the state, causing more fatal overdoses than all other prescription opioid products combined.[257] The high prevalence of circumvented methadone prescriptions is likely due to the structure of the NC Medicaid benefit. Methadone, when indicated for opioid use disorder treatment, is only covered for beneficiaries with managed care NC Medicaid coverage.[258] Methadone, when indicated for pain management, however, is covered for beneficiaries with either NC Medicaid's managed care or fee-for-service coverage. Therefore, NC Medicaid fee-for-service beneficiaries prescribed methadone for treatment of an opioid use disorder would be forced to pay for these prescriptions entirely out-of-pocket, resulting in an elevated prevalence of circumvented methadone fills. Further investigation outside the scope of this dissertation is needed to assess whether NC MLIP enrollees with fee-for-service coverage experienced access barriers to methadone therapy for opioid misuse therapy. Regardless, it is imperative that future efforts to mitigate MLIP circumvention focus on establishing greater oversight of methadone use among MLIP enrollees due to its elevated risk for overdose outcomes.

Addressing the problem of MLIP circumvention will be necessary for MLIPs to achieve their stated public health goals. Strategies to reduce MLIP circumvention could take many forms. First, MLIP administrators should provide better education to lock-in providers about their roles in maintaining the care coordination network for their MLIP patients. A recent survey of North Carolina pharmacists by the dissertation parent project team found that pharmacist providers of MLIP enrollees explicitly requested improved communication from MLIP administrators to alleviate what they perceived as a lack of knowledge about the MLIP's purpose and process.[259] Provider education could include additional training on and/or requirements for providers to use PDMP resources in the course of care delivery to their MLIP patients. Standardized use of PDMPs would allow identification of circumvention behavior and give providers the opportunity to take steps to correct instances of unnecessary care duplications or report suspected diversion activities to program administrators.

MLIP circumvention may also be mitigated through patient-centered interventions. First, MLIP administrators should consider delivering enhanced education at the time of MLIP enrollment. Currently, NC MLIP enrollees receive a letter in the mail 30 days prior to their MLIP enrollment informing them that their access to controlled substance-related services is being restricted to a single prescriber and pharmacy. This represents a missed opportunity to convey to the underlying purpose behind MLIP enrollment as being motivated by a desire for improved quality and not disciplinary in nature. Extending the idea of reframing the MLIP as a tool for care quality as opposed to punishment, existing MLIPs could serve as platforms for building patient-centered medical home-type programs focused on high quality collaborative care, specifically for substance use, pain, and mental health disorders. Indiana and Montana currently operate potential exemplar models for collaborative, patient-centered MLIPs that utilize case managers and primary care providers as medical home centers whose purpose it is refer MLIP enrollees to needed ancillary services, such as substance use or chronic pain treatment, which are covered by Medicaid.[260,261]

Our research in Aims 1 and 2 demonstrates the benefit of pursuing integrated data systems in evaluating and administering the NC MLIP. To our knowledge, these studies represented the first efforts

in the peer-reviewed literature to link administrative claims data with PDMP records. This allowed unprecedented observation of comprehensive controlled substance-seeking behaviors among Medicaid beneficiaries. If deployed effectively in the healthcare delivery process, this new information would greatly enhance prescribers' and pharmacists' ability to monitor high-risk controlled substance use behaviors, including MLIP circumvention, and take steps correct it, if necessary. For example, implementing automated cross-checking of PDMP data and MLIP enrollment records into pharmacies' prescription processing software would provide pharmacists would alert pharmacists to circumvention behavior without disrupting existing workflow. Policymakers, payers, and providers must make integrated PDMP systems a national priority, both in terms of cooperation with data streams from payers and cooperation with data systems across state lines.[8,10,25-28]

5.3.3 Policy Implications—MLIP Eligibility Criteria

In Aim 3, we evaluated the predictive performance of high-risk opioid use criteria. We mimicked how these types of measures are currently applied in the NC MLIP to get a sense for how effective this MLIP eligibility assessment approach is at enrolling individuals at the greatest risk for relevant public health outcomes from prescription drug abuse.

Ultimately, our claims-based opioid exposure measures performed poorly at predicting overdose and substance use disorder outcomes. The number of unique opioid-dispensing pharmacies, despite being included in multiple MLIP programs' eligibility criteria[147], failed to discriminate between subjects experiencing the outcomes and those that did not among opioid users in NC Medicaid. Even though the measures of number of opioid prescription fills and mean MME/day over a 60-day period were evaluated in the validation phase of Aim 3, neither of them proved to be very sensitive both alone or in combination. For example, the ≥5 opioid fill criterion flagged 5,525 subjects as high-risk for accidental opioid overdose, but it still only captured 26% of the 174 overdose events observed during the study period.

This poor performance by our selected high-risk opioid use criteria could be attributable to a few underlying causes. First, it is possible there simply exists a low performance ceiling for any claims-based measure of high-risk opioid use in predicting prescription drug overdose outcomes. The causes of overdose events may be too multifactorial to be captured in the limited scope of administrative claims data. Notably, Medicaid claims cannot capture the contributions of illicit drug use to overdose events, which has experienced growing prevalence among nonmedical prescription drug users in recent years.[262] As demonstrated in Aim 1, Medicaid claims also fail to capture highly prevalent controlled substance circumvention behavior that would contribute to adverse prescription drug abuse outcomes. Also, the 60-day opioid exposure window we used to simulate NC Medicaid eligibility assessment may have been too short for thorough assessment of opioid use risk. Much of the existing literature regarding claims-based prescription abuse risk factors employed assessment periods of 90-365 days.[140,141,151,155,161,169] This might explain why the measures of unique opioid dispensing pharmacies failed to discriminate subjects with overdose events in Aim 3. Pharmacy count measures shown to be predictive of relevant public health outcomes typically used an assessment period of 6-12 months in prior studies.[151,152,157,158,162] Lastly, the application of NC MLIP eligibility criteria and the opioid use criteria in Aim 3 analyses did not adjust for patient-level characteristics known to be associated with nonmedical opioid use and related outcomes. Most of the existing literature examining optimal claims-based measures of high-risk opioid use controlled for factors like age, sex, and clinical characteristics, despite this not being standard practice in real-world MLIP operations.[140,141,144,161] For example, optimal MLIP eligibility criteria may need to account for differences between the sexes, age categorizations, and the presence of certain baseline clinical diagnoses, particularly mental health conditions.

The fact that even the best claims-based measures of high-risk opioid use in Aim 3 performed poorly precluded our ability to confidently and definitively recommend specific binary opioid use measures in assessing MLIP eligibility. New and actionable evidence for concrete claims-based measures of high-risk opioid use is needed before this can take place. Our Aim 3 findings illuminate the large role that subjectivity will play when MLIP administrators craft MLIP eligibility criteria. In this situation, two

key trade-offs must be considered: 1) Program capacity vs. desired sensitivity, and 2) Rapid vs. thorough risk assessment.

Aim 3 analyses clearly indicated that the sensitivity of high-risk opioid use criteria in capturing subjects who experienced an overdose had a strong positive relationship with the number of subjects flagged by that measure. Therefore, MLIP administrators must assess the extent to which they intend the MLIP to act as a tool for preventing adverse public health outcomes (favor increased program enrollment capacity and high sensitivity) or as a tool primarily for preventing waste and fraudulent use of Medicaid resources (favor low program enrollment and high specificity).[130] Additionally, MLIP administrators face a difficult decision regarding length of the eligibility assessment period. Shorter assessment periods, such as North Carolina's two-month assessment, allows for more rapid identification of high-risk opioid use, and therefore timelier enrollment of high-risk beneficiaries in the MLIP. However, the poor performance of our 60-day measures, as well as the body of literature using assessment periods of 90 days and greater, suggest that claims-based measures of high-risk opioid use may perform better at predicting overdose events when assessed over periods of three months or more.

Moving forward, existing MLIPs should carefully reevaluate their approaches to assessing MLIP eligibility. The high prevalence of this policy strategy across the country means MLIPs are poised to play a useful role in the fight against prescription drug abuse in Medicaid. For this to come to fruition, though, a concerted effort is needed on behalf of administrators and policymakers to optimize MLIPs for achieving public health outcomes. A primary mechanism for optimizing MLIPs is through enrolling beneficiaries that stand to benefit the most from the MLIP intervention, and enrolling enough of them to have the opportunity to cause meaningful reductions in overdose and substance use disorder outcomes. In this spirit, MLIP administrators should prioritize use of MLIP eligibility criteria that maximize sensitivity for capturing preventable prescription drug abuse outcomes.

MLIP administrators should also explore alternative approaches to assessing eligibility outside of the current practice of multiple dichotomous claims-based measures that improve the sensitivity for capturing relevant, preventable prescription drug abuse outcomes. More intricate algorithmic approaches

may be appropriate, which can assess multiple conditional criteria simultaneously and account for relevant patient-level predictors.[150] Opioid risk scoring methods may also have added benefit through its assessment and weighting of multiple claims-based measures of controlled substance use.[168] If claims-based approaches to assessing MLIP eligibility continue to perform poorly at identifying patients at high risk for preventable overdose events, then it may be necessary to rely more heavily on provider referrals. Providers' professional judgment can account for more nuanced risk factors exhibited by patients that would not be measurable in claims data, such as illicit substance use or significant history of nonmedical controlled substance use in the patient's household. However, the human element of provider referrals could introduce inappropriate biases in identifying MLIP enrollees, so additional processes for independent vetting of provider referrals would be necessary to mitigate discriminatory MLIP enrollment practices.

5.3.4 Policy Implications—Call to Action

Taken as a whole, this dissertation highlights four necessary steps to achieve optimal public health benefit of the MLIP policy strategy in combatting prescription drug abuse:

1. Foster a unified perception among payers, policymakers, providers, and patients that MLIPs are foremost a public health intervention, not a cost-savings intervention.
2. Protect the integrity of the MLIP's intended enhanced care coordination by reducing MLIP circumvention behavior through, potentially, MLIP provider and enrollee education interventions, integration of smarter and cooperative health care data systems into medical and pharmacy practice, and medical home-type MLIP designs.
3. Employ MLIP eligibility criteria that maximize enrollment of—and subsequently, the sensitivity for capturing—beneficiaries with the greatest risk for adverse clinical outcomes from high-risk prescription drug use.
4. Build a body of rigorous, scientific evidence for the effectiveness of the MLIP intervention strategy in achieving desired public health outcomes. Efforts to reduce circumvention and optimize MLIP eligibility criteria will be moot if there is not any clear consensus that the

underlying premise of the MLIP policy of restricting access provider access for controlled substance services actually reduces prescription drug abuse, diversion, and overdose events without presenting unintended barriers to healthcare.

5.4 LIMITATIONS

Findings from this dissertation should be considered in light of several limitations with regard to generalizability, study data, and analyses. These results may have limited utility for similar policy applications in private payer or other public insurance settings other than Medicaid programs. While it is hoped that this dissertation provides new evidence for MLIPs as a general policy strategy, these findings only directly generalize to the NC MLIP and the NC Medicaid patient population. These results may not apply to other states with varying MLIP designs and patient demography. The use of analytic cohorts in Aims 1 and 2 with extended periods of continuous NC Medicaid coverage may not be representative of the broader Medicaid population, which is known to experience high enrollment turbulence.[212]

NC CSRS records were not available for the full NC Medicaid population, precluding the opportunity to compare circumvention behavior patterns with a control group that did not experience the MLIP intervention. The CSRS was unable to observe controlled substance use outside of North Carolina's state boundaries. However, Aims 1 and 2 analyses attempted to control for this by including a dummy covariate indicating residence in a border county. The CSRS also failed to capture 6% of controlled substance fills, as evidenced by 6% of Medicaid claims lacking a corresponding CSRS record. Although these missing CSRS records appeared to be missing at random with respect to key measures, this less-than-perfect capture rate likely led to our estimates of circumvention prevalence to be artificially low.

Medicaid prescription claims data provided by NC DMA lacked variables allowing ascertainment of unique prescribers. This prevented construction of an indicator of MLIP eligibility due to ≥4 unique controlled substance prescribers in Aims 1 and 2 as well as a measure of number of unique opioid prescribers in Aim 3 analyses. To address this limitation, proxy measures of number of unique community/outpatient pharmacies constructed to attempt to capture the variation in key outcomes

explained by high utilization of controlled substance providers. As with any research using administrative prescription claims data, we were only able to observe dispensing of medications. Prescription claims data does not allow measurement of actual medication use and cannot capture use of substances by study subjects that were obtained through routes not captured by these data sources—whether prescription or illicit substances. Claims data may also suffer from misclassification of exposures and outcomes, as it relies on accurate upstream input from providers administering those services.

Estimates produced by statistical models in all dissertation aims can only be interpreted as associations between predictors and outcomes and not as causal relationships. These estimates may also be biased by variable misspecification or failure to control for unknown and/or unmeasurable confounders. Potential unmeasurable confounders included full prescription cost data, household controlled substance use patterns, unique prescribers, prescriber skill/training, detailed geospatial relationships, education, concomitant prescription and illicit substance use not captured by study data, patient frailty, and health beliefs. Secular trends in the prescription drug market and medical practice were also not observable. However, we attempted to account for these in Aims 1 and 2 models by controlling for historical time. Aim 3 analyses were also limited by the inability to observe unintentional overdose outcomes, particularly fatal overdose events, that did not result in contact with the healthcare system and subsequently generate Medicaid claims records for treatment.

5.5 FUTURE RESEARCH

This dissertation represented one of the first attempts to establish a peer-reviewed evidence base for understanding and bolstering MLIP effectiveness in improving public health outcomes related to prescription drug abuse. There exist many rich opportunities to build on the research presented here to advance knowledge in this area.

Aim 1 provided a population-level view of circumvention behavior after enrollment in the NC MLIP. However, it would also be valuable to garner further understanding of the differences between groups of MLIP enrollees who exhibit no circumvention behavior and those that exhibit high circumvention behavior after MLIP enrollment. For example, a study of circumvention behavior

"trajectories" over time using explanatory factor analysis could elucidate greater understanding of patient-level predictors, and potentially root causes, for not adhering to MLIP restrictions.

Additionally, future research should incorporate elements lacking from the present studies due to limitations in the study data sources. Linking CSRS data to the full NC Medicaid population would allow investigation of Medicaid circumvention behavior as a predictor of preventable overdose outcomes. Findings from this research would not only further inform our understanding of the consequences of circumvention in the context of MLIPs but also allow circumvention behavior to be employed as a potential measure of high-risk behavior in MLIP eligibility criteria applications. Out-of-pocket costs of controlled substance medications likely played a role as a predictor of circumvention behavior, but CSRS data lacked a payment field to assess this confounder. Further investigation of MLIP circumvention should incorporate prescription cost to better understand the role it plays in predicting which prescriptions are circumvented and the financial burden placed on low-income Medicaid beneficiaries by circumvention. Similarly, the present study data lack geographic characteristics more granular than the county-level. A growing body of literature has demonstrated the importance of geographic relationships between patients, prescribers, and pharmacies in predicting nonmedical prescription drug use patterns.[22,263,264] Being able to assess exact distances between patients and providers will allow us to recognize and ultimately correct potential geographic barriers to maintaining an MLIP's enhanced care coordination. The momentum behind PDMP and data resource interoperability will provide valuable opportunities to research interstate controlled substance use behaviors. This will have special importance for fully characterizing circumvention behaviors, because the CSRS data was limited to North Carolina-specific activity and incapable of capturing prescriptions filled across state lines.

Results from Aim 1 and 2 highlight the need to examine the extent to which MLIP enrollment may impose undue barriers to care for patients with legitimate need. Engaging in qualitative, primary data collection of patient-reported outcomes would provide a valuable chance to identify enrollee motivations for engaging in circumvention, whether it be motivated by abuse/diversion intentions or unintended barriers to care stemming from MLIP provider restrictions. Additionally, the NC MLIP restrictions only

apply to opioid analgesics and benzodiazepines. It is unknown if, and to what extent, MLIP restrictions for these two controlled substance medication classes causes "spillover" effects on accessibility and utilization of other medication classes not directly regulated by the MLIP. This will be especially important to understand for MLIP enrollees with chronic disease, such as those with cardiovascular disease, hyperlipidemia, and diabetes, whose overall health outcomes require optimal adherence to non-controlled medication classes.

Much discussion was also presented in this dissertation for the potential role of MLIP provider and enrollee educational interventions for reducing MLIP circumvention. Intervention studies will be needed to develop, validate, and evaluate such interventions intended to empower lock-in providers with the knowledge and tools to monitor and deliver quality care to MLIP enrollees. MLIP enrollee education interventions would be designed to clearly convey that the purpose of the MLIP is to deliver higher quality care and prevent unnecessary health outcomes from high-risk medication use as well as provide enrollees with clear direction for how to navigate the healthcare system when enrolled in the MLIP.

Many opportunities also exist to build on the work of Aim 3 in bolstering MLIP eligibility assessment methods that identify beneficiaries at the highest risk for adverse clinical outcomes from high-risk controlled substance use. Logical next steps from Aim 3 would be to investigate varied opioid exposure periods beyond two months, which is currently in use in North Carolina. Additional work should be done employing advanced predictive modeling techniques. The prescription drug abuse literature clearly demonstrates that nonmedical use behaviors and outcomes are multifaceted in their origin, which is not currently reflected in state Medicaid agencies' approach to defining "high-risk" in the MLIP context. It may also be useful to conduct these more advanced predictive modeling studies among Medicare and privately insured patient populations, not only to broaden external validity to other patient populations, but also to capitalize on the vast size of these populations that would improve the quality of predictive modeling studies for key outcomes that are relatively rare, like opioid overdose events. Future research should also look to alternative data sources, such as electronic medical records, to construct measures of high-risk controlled substance use. A recent study from Hylan, et al, used natural language

processing techniques in electronic medical record data to construct risk measures with substantially higher discriminatory power and sensitivity for predicting problematic opioid use outcomes compared to our single claims-based measure criteria.[265]

Lastly, Aim 3 focused on the most pertinent clinical outcomes from high-risk opioid use. A natural extension of this study would be to conduct a cost-effectiveness analysis of MLIP interventions, accounting for costs of administering the program, costs of controlled substance-related services, and costs of downstream adverse outcomes from high-risk opioid use. This would provide a comprehensive perspective of the role of MLIPs in the fight against the prescription drug abuse epidemic, by recognizing its function as a tool to improve public health outcomes while also acknowledging the importance of financial sustainability to MLIP administrators.

5.6 CONCLUSION

Despite these limitations and opportunities for future research, the research presented in this dissertation represents one of the first contributions to a body of peer-reviewed evidence for the effectiveness and optimal design of MLIPs in preventing prescription drug abuse. Specifically, this is the first study, to our knowledge, quantifying the effect of MLIP enrollment on controlled substance circumvention behavior through linkage of Medicaid claims and state PDMP data. In Aim 1, enrollment in the NC MLIP was associated with a 3.6 times higher likelihood of obtaining a controlled substance prescription through circumvention compared to months before MLIP enrollment, controlling for patient and policy characteristics. Although the MLIP caused the frequency of circumvention to increase, in Aim 2 we demonstrated that circumvented opioid prescription use was no riskier at the prescription level after subjects were enrolled in the MLIP. In Aim 3, the claims-based opioid use measure approach to assessing MLIP eligibility in the NC MLIP was shown to have poor performance in capturing NC Medicaid beneficiaries at the highest risk for experiencing preventable overdose outcomes. Findings from this dissertation will inform NC MLIP optimizations to improve its public health benefit. On a larger scale, it is hoped these findings will also enhance the effectiveness of targeted, comprehensive, and patient-centered policy interventions across the country intended to combat the prescription drug abuse epidemic.

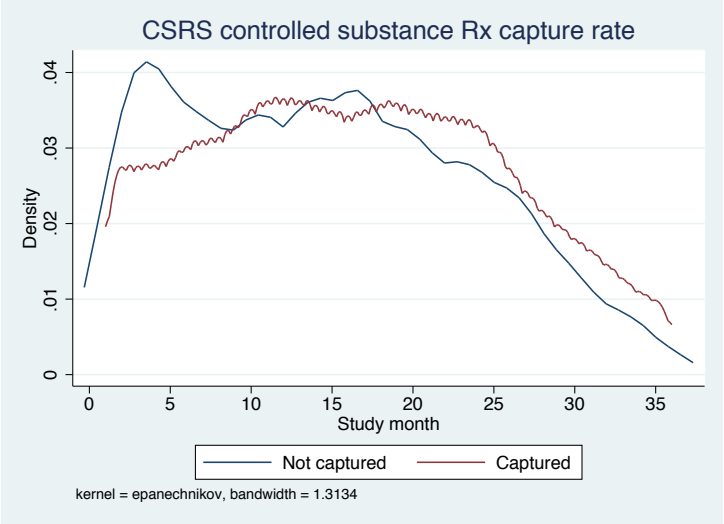
APPENDIX

Appendix Table 1: Examining differences in characteristics of Medicaid controlled substance claims captured by the CSRS vs. not captured by the CSRS

	Total	Captured	Not captured	p
Age in years, mean (SD)	40.4 (10.4)	40.2 (10.4)	42.3 (10.6)	0.000
Female, %	72.7%	72.6%	73.2%	0.303
County RUCC score, mean (SD)	2.67 (1.78)	2.66 (1.77)	2.87 (1.92)	0.000
Charlson score, mean (SD)	1.51 (2.05)	1.50 (2.05)	1.55 (2.04)	0.122
Schedule II opioid, %	60.5%	60.4%	62.3%	0.003
Long acting opioid, %	17.7%	17.5%	21.1%	0.000
Prescribed MME/day, mean (%)	79.7 (132)	79.4 (131)	84.2 (145)	0.007

Note: CSRS=Controlled Substances Reporting System; SD=Standard deviation; RUCC=Rural-Urban Continuum Code; MME=Milligram morphine equivalent. Higher RUCC score indicates more rural.

Appendix Figure 1: Distribution of captured vs. non-captured controlled substance prescription claims in the CSRS across the Aim 1 and 2 study period



Note: CSRS=Controlled Substances Reporting System

Appendix Table 2: NC Medicaid coverage gaps in the Aim 1 analytic cohort

Month-long coverage gaps	Frequency n (%)	Cumulative %
0	1528 (92.8%)	92.8%
1	109 (6.6%)	99.4%
2	10 (0.6%)	100.0%

Appendix Table 3: Sensitivity analysis results of generalized estimating equation models of circumvention behavior after excluding Aim 1 subjects with any gaps in Medicaid coverage

	Any circumvented fill			Number of circumvented fills		
Variable	RR	(95% CI)	P-value	IRR	(95% CI)	P-value
Key independent variable						
MLIP enrollment (Key IV)	3.59	(3.15, 4.10)	<0.001	4.50	(3.82, 5.30)	<0.001
MLIP policy variables						
MLIP enrollment * month	1.00	(0.99, 1.01)	0.895	1.01	(1.00, 1.02)	0.201
MLIP enrollment delay	1.29	(1.13, 1.48)	<0.001	1.25	(1.06, 1.48)	0.008
MLIP enrollment delay * month	1.02	(1.00, 1.04)	0.035	1.02	(1.00, 1.05)	0.046
Month	1.00	(0.99, 1.01)	0.606	0.98	(0.97, 1.00)	0.023
MLIP policy period	0.82	(0.73, 0.92)	0.001	0.87	(0.75, 1.00)	0.049
MLIP policy period * month	0.99	(0.98, 1.00)	0.100	1.00	(0.98, 1.01)	0.657
MLIP eligibility route						
Opioid use	1.01	(0.87, 1.17)	0.902	1.13	(0.95, 1.35)	0.169
Benzodiazipine use	1.51	(1.28, 1.79)	<0.001	1.79	(1.47, 2.17)	<0.001
Prescriber use	1.10	(1.00, 1.20)	0.053	1.16	(1.01, 1.34)	0.042
No eligibility criteria met	0.95	(0.72, 1.25)	0.712	1.00	(0.70, 1.43)	0.988
Predisposing characteristics						
Age	0.993	(0.99, 1.00)	<0.001	0.992	(0.99, 1.00)	0.007
Female	0.93	(0.86, 1.02)	0.124	0.88	(0.77, 1.00)	0.058
Race (White referent)						
Black	0.99	(0.90, 1.10)	0.900	0.96	(0.82, 1.13)	0.643
Other	0.99	(0.84, 1.15)	0.853	0.95	(0.76, 1.18)	0.630
Enabling characteristics						
Metropolitan residence	1.00	(0.91, 1.09)	0.969	1.03	(0.90, 1.17)	0.678
County pharmacy supply (<10 referent)						
11-25	1.06	(0.95, 1.19)	0.282	1.05	(0.90, 1.22)	0.551
26-50	1.11	(1.00, 1.24)	0.057	1.09	(0.94, 1.27)	0.270
51-100	1.10	(0.98, 1.24)	0.116	1.07	(0.91, 1.26)	0.429
>100	1.25	(1.09, 1.43)	0.002	1.37	(1.10, 1.70)	0.006
Border county	0.97	(0.90, 1.05)	0.440	0.98	(0.87, 1.11)	0.751
Need characteristics						
Chronic non-cancer pain	1.33	(1.04, 1.70)	0.026	1.46	(1.08, 1.99)	0.015
Anxiety disorder	1.14	(1.05, 1.24)	0.002	1.12	(0.99, 1.28)	0.077
Substance abuse disorder	1.02	(0.94, 1.09)	0.694	1.04	(0.93, 1.17)	0.466
Depression	1.08	(1.00, 1.17)	0.064	1.12	(0.99, 1.27)	0.063
Other mental illness	1.03	(0.96, 1.11)	0.379	1.02	(0.91, 1.14)	0.729
Charlson Comorbidity Index score						
0 (referent)						
1	1.00	(0.91, 1.09)	0.998	0.97	(0.85, 1.11)	0.668
≥2	1.15	(1.04, 1.27)	0.007	1.17	(0.99, 1.37)	0.060
Prescription drug burden	1.00	(0.99, 1.00)	0.431	1.00	(0.99, 1.01)	0.402

Note: 1,528 subjects were included (119 excluded due to a coverage gap of 1 or 2 months). RR=Relative risk; CI=Confidence interval; IRR=Incidence rate ratio; MLIP=Medicaid controlled substance lock-in program

Appendix Table 4: Sensitivity analysis comparing generalized estimated equation output from logistic versus modified Poisson modeling approach of the Aim 1 binary circumvention outcome

	Modified Poisson			Logistic regression		
Variable	RR	(95% CI)	P-value	OR	(95% CI)	P-value
Key independent variable						
MLIP enrollment (Key IV)	3.55	(3.13, 4.03)	<0.001	5.96	(5.05, 7.03)	<0.001
MLIP policy variables						
MLIP enrollment * month	1.00	(0.99, 1.01)	0.675	1.00	(0.98, 1.01)	0.550
MLIP enrollment delay	1.28	(1.13, 1.46)	<0.001	1.33	(1.14, 1.56)	<0.001
MLIP enrollment delay * month	1.02	(1.00, 1.03)	0.031	1.03	(1.00, 1.05)	0.018
Month	1.00	(0.99, 1.01)	0.766	1.00	(0.99, 1.01)	0.845
MLIP policy period	0.81	(0.73, 0.91)	<0.001	0.80	(0.70, 0.92)	0.001
MLIP policy period * month	0.99	(0.98, 1.00)	0.099	0.98	(0.96, 1.00)	0.037
MLIP eligibility route						
Opioid use	1.01	(0.87, 1.16)	0.928	1.01	(0.81, 1.25)	0.932
Benzodiazipine use	1.52	(1.29, 1.79)	<0.001	2.01	(1.49, 2.70)	<0.001
Prescriber use	1.10	(1.01, 1.21)	0.028	1.16	(1.02, 1.32)	0.028
No eligibility criteria met	0.94	(0.72, 1.22)	0.628	0.91	(0.62, 1.34)	0.646
Predisposing characteristics						
Age	0.994	(0.99, 1.00)	0.001	0.99	(0.99, 1.00)	0.002
Female	0.94	(0.86, 1.02)	0.144	0.91	(0.80, 1.03)	0.147
Race (White referent)						
Black	0.99	(0.90, 1.10)	0.892	0.99	(0.85, 1.15)	0.889
Other	0.96	(0.82, 1.11)	0.551	0.94	(0.75, 1.17)	0.569
Enabling characteristics						
Metropolitan residence	1.01	(0.93, 1.10)	0.806	1.02	(0.90, 1.16)	0.776
County pharmacy supply (<10 referent)						
11-25	1.05	(0.95, 1.17)	0.343	1.08	(0.92, 1.26)	0.340
26-50	1.10	(0.99, 1.22)	0.071	1.15	(0.99, 1.34)	0.072
51-100	1.07	(0.96, 1.20)	0.220	1.11	(0.94, 1.31)	0.237
>100	1.22	(1.07, 1.39)	0.004	1.34	(1.10, 1.64)	0.004
Border county	1.00	(0.93, 1.07)	0.925	0.99	(0.89, 1.11)	0.916
Need characteristics						
Chronic non-cancer pain	1.33	(1.06, 1.68)	0.013	1.50	(1.10, 2.04)	0.010
Anxiety disorder	1.12	(1.04, 1.22)	0.003	1.19	(1.06, 1.33)	0.003
Substance abuse disorder	1.01	(0.94, 1.08)	0.874	1.01	(0.91, 1.12)	0.855
Depression	1.07	(0.99, 1.16)	0.071	1.11	(0.99, 1.24)	0.070
Other mental illness	1.05	(0.98, 1.13)	0.195	1.07	(0.96, 1.19)	0.208
Charlson Comorbidity Index score						
0 (referent)						
1	1.00	(0.92, 1.09)	0.979	1.00	(0.88, 1.13)	0.995
≥2	1.14	(1.03, 1.25)	0.010	1.21	(1.05, 1.41)	0.011
Prescription drug burden	1.00	(0.99, 1.00)	0.473	1.00	(0.99, 1.00)	0.458

Note: RR=Relative risk; OR=odds ratio; CI=confidence interval; IRR=incidence rate ratio; MLIP=Medicaid lock-in program. OR were obtained through generalized estimating equation (GEE) modeling with monthly measures using binomial distribution, logit link, and autoregressive (1 month) correlation structure. RR were obtained through GEE using Poisson distribution, log link, and autoregressive correlation structure. Both models used robust standard errors.

Appendix Table 5: Pearson's correlation coefficients among enabling variables in Aim 1

	RUCC	Metro county	Pharmacy supply	Prescriber supply	Border county
RUCC	1.00				
Metro county	-0.85	1.00			
Pharmacy supply	-0.45	0.35	1.00		
Prescriber supply	-0.42	0.38	0.92	1.00	
Border county	0.13	-0.26	0.10	-0.01	1.00

Note: All enabling variables assessed at county level. RUCC=Rural-urban continuum code

Appendix Table 6: Pearson's correlation coefficients among need variables in Aim 1

	Pain	Anx -iety	Depress -ion	Subst. use	Other MHI	Charl -son	Rx count	Opioid elig.	Benzo elig.	Doc elig.	Not elig.
Pain	1.00										
Anxiety	0.10	1.00									
Depression	0.07	0.28	1.00								
Subst. use	0.04	0.17	0.16	1.00							
Other MHI	0.05	0.23	0.24	0.19	1.00						
Charlson	0.09	0.05	0.12	0.13	0.05	1.00					
Rx count	0.20	0.24	0.30	0.10	0.22	0.36	1.00				
Opioid elig.	0.06	-0.09	-0.08	-0.14	-0.12	0.04	0.06	1.00			
Benzo elig.	-0.03	0.10	0.05	0.05	0.07	0.02	-0.04	-0.31	1.00		
Doc elig.	0.03	-0.01	-0.09	0.00	-0.05	-0.13	-0.24	0.12	0.00	1.00	
Not elig.	-0.09	0.04	0.06	0.13	0.06	-0.02	-0.01	-0.59	-0.04	-0.33	1.00

Note: Subst.=Substance; MHI=Mental health illness; Rx=Prescription; Elig=Eligibility; Benzo=Benzodiazepine; Doc=Prescriber.

Appendix Table 7: Distribution of a categorical county-level pharmacy supply measure in the Aim 1 cohort

County pharmacy supply	Frequency n (%)	Cumulative %
10 or less	9144 (17.7%)	17.7%
11 to 25	12680 (24.5%)	42.1%
26 to 50	13362 (25.8%)	67.9%
51 to 100	10186 (19.7%)	87.6%
Over 100	6426 (12.4%)	100.0%

Note: County pharmacy supply was variable within subject, so frequency refers to monthly observations

Appendix Table 8: Sensitivity analysis results of generalized estimating equation models of circumvention behavior when including county-level pharmacy supply, county RUCC score, and Charlson score in their original continuous forms

	Any circumvented fill			Number of circumvented fills		
Variable	RR	(95% CI)	P-value	IRR	(95% CI)	P-value
Key independent variable						
MLIP enrollment (Key IV)	3.54	(3.12, 4.02)	<0.001	4.39	(3.74, 5.14)	<0.001
MLIP policy variables						
MLIP enrollment * month	1.00	(0.99, 1.01)	0.656	1.01	(0.99, 1.02)	0.282
MLIP enrollment delay	1.28	(1.13, 1.46)	<0.001	1.25	(1.06, 1.47)	0.008
MLIP enrollment delay * month	1.02	(1.00, 1.03)	0.033	1.02	(1.00, 1.05)	0.038
Month	1.00	(0.99, 1.01)	0.763	0.98	(0.97, 1.00)	0.025
MLIP policy period	0.81	(0.73, 0.91)	<0.001	0.88	(0.77, 1.01)	0.078
MLIP policy period * month	0.99	(0.98, 1.00)	0.104	1.00	(0.98, 1.01)	0.661
MLIP eligibility route						
Opioid use	1.01	(0.87, 1.16)	0.932	1.11	(0.93, 1.32)	0.263
Benzodiazipine use	1.55	(1.31, 1.82)	<0.001	1.83	(1.51, 2.21)	<0.001
Prescriber use	1.10	(1.01, 1.21)	0.030	1.18	(1.03, 1.35)	0.019
No eligibility criteria met	0.93	(0.71, 1.21)	0.576	0.96	(0.68, 1.36)	0.828
Predisposing characteristics						
Age	0.994	(0.99, 1.00)	0.002	0.994	(0.99, 1.00)	0.018
Female	0.94	(0.86, 1.02)	0.159	0.88	(0.78, 1.00)	0.058
Race (White referent)						
Black	0.99	(0.89, 1.09)	0.802	0.96	(0.82, 1.12)	0.582
Other	0.97	(0.84, 1.13)	0.728	0.92	(0.75, 1.14)	0.450
Enabling characteristics						
RUCC score	0.99	(0.97, 1.01)	0.415	0.99	(0.96, 1.02)	0.654
County pharmacy supply	1.00	(1.00, 1.00)	0.030	1.00	(1.00, 1.00)	0.014
Border county	0.99	(0.92, 1.06)	0.721	1.00	(0.89, 1.11)	0.948
Need characteristics						
Chronic non-cancer pain	1.34	(1.07, 1.69)	0.012	1.48	(1.11, 1.97)	0.007
Anxiety disorder	1.13	(1.05, 1.22)	0.002	1.12	(0.99, 1.26)	0.079
Substance abuse disorder	1.01	(0.94, 1.08)	0.866	1.03	(0.92, 1.15)	0.624
Depression	1.07	(0.99, 1.15)	0.097	1.10	(0.98, 1.24)	0.094
Other mental illness	1.05	(0.97, 1.12)	0.221	1.03	(0.93, 1.15)	0.572
Charlson Comorbidity Index score	1.03	(1.01, 1.05)	0.002	1.03	(1.01, 1.06)	0.019
Prescription drug burden	1.00	(0.99, 1.00)	0.424	1.00	(0.99, 1.00)	0.368

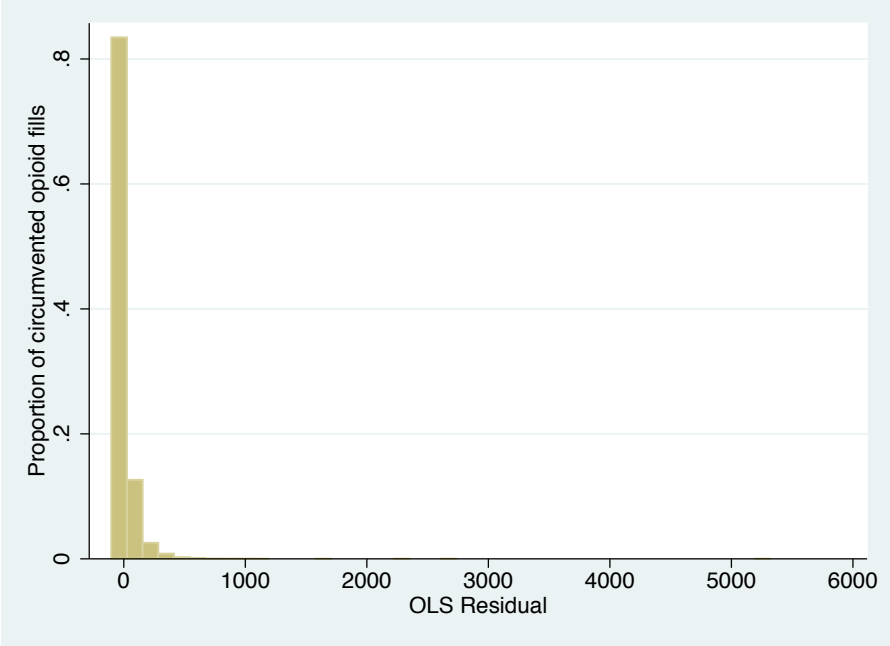
Note: RR=Relative risk; CI=Confidence interval; IRR=Incidence rate ratio; MLIP=Medicaid controlled substance lock-in program; RUCC=Rural-urban continuum code (RUCC ranges from 1-9 with 1 reflected the most metropolitan counties)

Appendix Table 9: GLM models for Aim 2 outcomes among circumvented opioid prescription fills, excluding subjects with coverage gaps

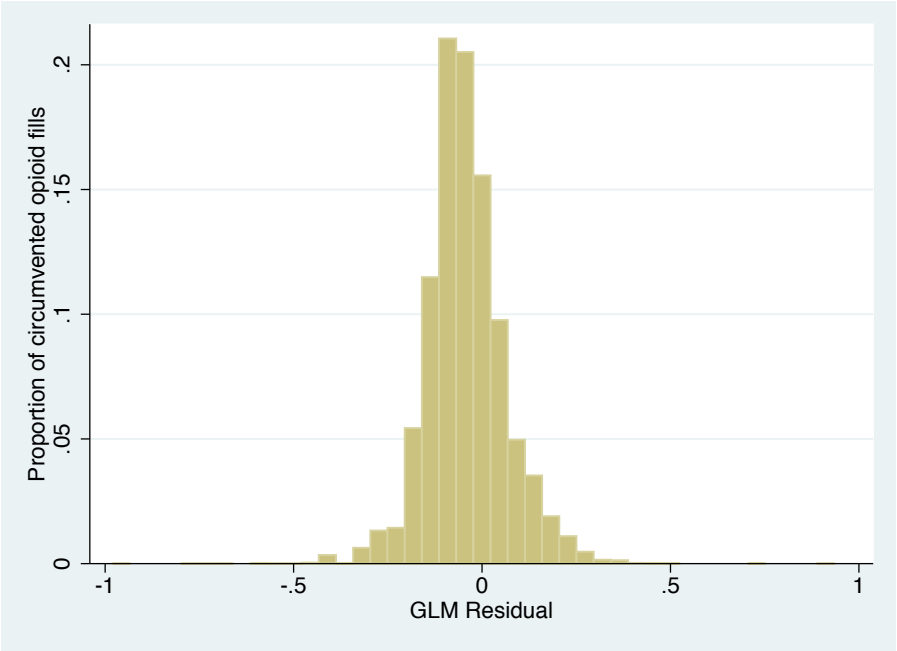
	Schedule II opioid			Long acting opioid			Mean MME/day		
Variable	**RR**	**(95% CI)**	**P-value**	**RR**	**(95% CI)**	**P-value**	**ME**	**(95% CI)**	**P-value**
Key independent variable									
MLIP enrollment	0.95	(0.84, 1.07)	0.406	0.53	(0.36, 0.78)	0.001	0.82	(-8.67, 10.32)	0.865
MLIP policy variables									
MLIP enrollment * month	1.00	(0.99, 1.02)	0.507	1.02	(0.98, 1.06)	0.257	0.42	(-0.41, 1.25)	0.324
MLIP enrollment delay	0.99	(0.88, 1.12)	0.860	0.80	(0.57, 1.11)	0.177	2.64	(-6.63, 11.92)	0.576
MLIP enrollment delay * month	1.00	(0.99, 1.02)	0.664	1.01	(0.96, 1.07)	0.676	0.76	(-0.80, 2.32)	0.340
Month	1.01	(1.00, 1.03)	0.055	1.00	(0.96, 1.04)	0.967	-0.61	(-1.68, 0.47)	0.272
MLIP policy period	1.06	(0.93, 1.19)	0.393	1.42	(1.03, 1.96)	0.032	-1.33	(-11.22, 8.55)	0.791
MLIP policy period * month	0.99	(0.97, 1.00)	0.059	1.00	(0.95, 1.05)	0.925	0.16	(-1.13, 1.44)	0.812
MLIP eligibility route									
Opioid use	0.96	(0.79, 1.17)	0.689	0.83	(0.50, 1.38)	0.473	2.96	(-10.26, 16.19)	0.661
Benzodiazepine use	0.90	(0.69, 1.16)	0.407	0.85	(0.43, 1.70)	0.656	-1.06	(-21.03, 18.91)	0.917
Pharmacy use	1.02	(0.92, 1.14)	0.675	0.90	(0.67, 1.21)	0.482	-1.55	(-8.94, 5.84)	0.681
No eligibility criteria met	1.04	(0.78, 1.38)	0.798	0.78	(0.27, 2.21)	0.639	-3.21	(-21.93, 15.51)	0.737
Predisposing characteristics									
Age	1.003	(0.998, 1.008)	0.199	1.007	(0.992, 1.021)	0.366	0.39	(0.07, 0.71)	0.018
Female	0.80	(0.73, 0.89)	<0.001	0.82	(0.59, 1.13)	0.233	-9.96	(-19.48 , -0.45)	0.040
Race (White referent)									
Black	1.09	(0.97, 1.23)	0.165	0.96	(0.65, 1.41)	0.820	-1.82	(-9.46, 5.81)	0.640
Other	1.11	(0.93, 1.32)	0.244	0.94	(0.51, 1.72)	0.840	-5.08	(-17.11, 6.95)	0.408
Enabling characteristics									
Metropolitan residence	0.92	(0.82, 1.03)	0.133	0.86	(0.60, 1.24)	0.416	-4.12	(-12.90, 4.67)	0.358
County pharmacy supply (<10 referent)									
11-25	0.95	(0.83, 1.09)	0.489	0.86	(0.55, 1.34)	0.501	-2.96	(-12.88, 6.96)	0.558
26-50	0.96	(0.85, 1.10)	0.574	0.96	(0.62, 1.49)	0.852	0.58	(-10.32, 11.49)	0.917
51-100	1.09	(0.94, 1.25)	0.243	1.14	(0.72, 1.80)	0.581	0.03	(-11.19, 11.25)	0.996
>100	0.91	(0.75, 1.11)	0.351	0.81	(0.47, 1.39)	0.436	-7.90	(-17.09, 1.30)	0.092
Border county	0.91	(0.82, 1.01)	0.073	1.08	(0.80, 1.46)	0.617	3.13	(-5.24, 11.49)	0.463
Need characteristics									
Chronic non-cancer pain	1.23	(0.94, 1.62)	0.134	4.70	(1.57, 14.09)	0.006	12.60	(3.86, 21.35)	0.005
Anxiety disorder	0.99	(0.90, 1.10)	0.899	0.90	(0.65, 1.25)	0.530	-3.10	(-10.81, 4.61)	0.430
Substance abuse disorder	1.01	(0.93, 1.11)	0.780	1.22	(0.90, 1.64)	0.198	2.68	(-3.78, 9.13)	0.417
Depression	1.14	(1.03, 1.26)	0.009	1.21	(0.89, 1.65)	0.218	1.44	(-5.68, 8.55)	0.692
Other mental illness	0.97	(0.87, 1.06)	0.477	0.89	(0.67, 1.20)	0.454	-0.92	(-7.98, 6.14)	0.799
Charlson Comorbidity Index (0 referent)									
1	1.03	(0.92, 1.15)	0.636	0.83	(0.56, 1.23)	0.352	5.32	(-3.01, 13.65)	0.211
≥2	1.12	(0.99, 1.27)	0.083	1.14	(0.77, 1.67)	0.516	15.17	(5.73, 24.61)	0.002
Prescription drug burden	1.00	(0.99, 1.00)	0.417	0.99	(0.98, 1.01)	0.359	-0.51	(-0.86 , -0.16)	0.005

Note: MME=Milligram morphine equivalent; RR=Relative risk; CI=Confidence interval; ME=Marginal effect; MLIP=Medicaid lock-in program. 117 subjects were excluded from primary analysis due Medicare coverage gap(s). GLM predicting the binary outcomes specified a Poisson distribution, log link, and cluster-robust standard errors. GLM predicting the mean MME/day outcome specified a log link, inverse Gaussian distribution, and cluster-robust standard errors. All models included 18,204 fills and 1,409 subjects.

Appendix Figure 2: Residual distribution for ordinary least squares model of level MME/day outcome



Appendix Figure 3: Residual distribution for GLM model of MME/day with inverse Gaussian distribution and log link



Appendix Table 10: Tabular survival ROC results—opioid fill count/unintentional opioid overdose

Opioid fill count cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
≥1	69668 (100.0%)	202 (0.3%)	1.00	0.00	0.00
≥2	35106 (50.4%)	152 (0.4%)	0.73	0.50	0.43
≥3*	19166 (27.5%)	117 (0.6%)	0.55	0.73	0.47
≥4	9712 (13.9%)	80 (0.8%)	0.38	0.86	0.36
≥5	5611 (8.1%)	60 (1.1%)	0.28	0.92	0.28
≥6	3316 (4.8%)	41 (1.2%)	0.20	0.95	0.19
≥7	1654 (2.4%)	20 (1.2%)	0.10	0.98	0.10
≥8	955 (1.4%)	14 (1.5%)	0.07	0.99	0.07
≥9	564 (0.8%)	9 (1.6%)	0.04	0.99	0.04
≥10	324 (0.5%)	6 (1.9%)	0.03	1.00	0.03
≥11	188 (0.3%)	3 (1.6%)	0.01	1.00	0.01
≥12	120 (0.2%)	1 (0.8%)	0.00	1.00	0.00
≥13	63 (0.1%)	0 (0.0%)	0.00	1.00	0.00
≥14	30 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥15	24 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥16	13 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥17	11 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥18	9 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥20	5 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥21	2 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥22	1 (0.0%)	0 (0.0%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 11: Tabular survival ROC results—opioid fill count/unintentional acetaminophen overdose

Opioid fill count cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
≥1	69668 (100.0%)	82 (0.1%)	1.00	0.00	0.00
≥2*	35106 (50.4%)	54 (0.2%)	0.64	0.50	0.38
≥3	19166 (27.5%)	37 (0.2%)	0.43	0.73	0.36
≥4	9712 (13.9%)	23 (0.2%)	0.27	0.86	0.26
≥5	5611 (8.1%)	18 (0.3%)	0.21	0.92	0.21
≥6	3316 (4.8%)	14 (0.4%)	0.16	0.95	0.16
≥7	1654 (2.4%)	10 (0.6%)	0.12	0.98	0.12
≥8	955 (1.4%)	5 (0.5%)	0.06	0.99	0.06
≥9	564 (0.8%)	2 (0.4%)	0.02	0.99	0.02
≥10	324 (0.5%)	2 (0.6%)	0.02	1.00	0.02
≥11	188 (0.3%)	2 (1.1%)	0.02	1.00	0.02
≥12	120 (0.2%)	1 (0.8%)	0.01	1.00	0.01
≥13	63 (0.1%)	0 (0.0%)	0.00	1.00	0.00
≥14	30 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥15	24 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥16	13 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥17	11 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥18	9 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥20	5 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥21	2 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥22	1 (0.0%)	0 (0.0%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 12: Tabular survival ROC results—opioid fill count/unintentional overdose, any drug

Opioid fill count cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
≥1	69668 (100.0%)	1040 (1.5%)	1.00	0.00	0.00
≥2	35106 (50.4%)	729 (2.1%)	0.68	0.50	0.40
≥3*	19166 (27.5%)	511 (2.7%)	0.46	0.73	0.40
≥4	9712 (13.9%)	323 (3.3%)	0.29	0.86	0.28
≥5	5611 (8.1%)	200 (3.6%)	0.18	0.92	0.18
≥6	3316 (4.8%)	134 (4.0%)	0.12	0.95	0.12
≥7	1654 (2.4%)	76 (4.6%)	0.07	0.98	0.07
≥8	955 (1.4%)	45 (4.7%)	0.04	0.99	0.04
≥9	564 (0.8%)	27 (4.8%)	0.03	0.99	0.03
≥10	324 (0.5%)	16 (4.9%)	0.01	1.00	0.01
≥11	188 (0.3%)	9 (4.8%)	0.01	1.00	0.01
≥12	120 (0.2%)	4 (3.3%)	0.00	1.00	0.00
≥13	63 (0.1%)	2 (3.2%)	0.00	1.00	0.00
≥14	30 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥15	24 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥16	13 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥17	11 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥18	9 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥20	5 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥21	2 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥22	1 (0.0%)	0 (0.0%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 13: Tabular survival ROC results—opioid fill count/opioid use disorder

Opioid fill count cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
≥1	69668 (100.0%)	2284 (3.3%)	1.00	0.00	0.00
≥2	35106 (50.4%)	1716 (4.9%)	0.74	0.51	0.44
≥3*	19166 (27.5%)	1280 (6.7%)	0.54	0.74	0.47
≥4	9712 (13.9%)	833 (8.6%)	0.35	0.87	0.34
≥5	5611 (8.1%)	565 (10.1%)	0.24	0.93	0.24
≥6	3316 (4.8%)	374 (11.3%)	0.16	0.96	0.16
≥7	1654 (2.4%)	213 (12.9%)	0.09	0.98	0.09
≥8	955 (1.4%)	123 (12.9%)	0.05	0.99	0.05
≥9	564 (0.8%)	73 (12.9%)	0.03	0.99	0.03
≥10	324 (0.5%)	44 (13.6%)	0.02	1.00	0.02
≥11	188 (0.3%)	34 (18.1%)	0.01	1.00	0.01
≥12	120 (0.2%)	22 (18.3%)	0.01	1.00	0.01
≥13	63 (0.1%)	13 (20.6%)	0.01	1.00	0.01
≥14	30 (0.0%)	6 (20.0%)	0.00	1.00	0.00
≥15	24 (0.0%)	6 (25.0%)	0.00	1.00	0.00
≥16	13 (0.0%)	2 (15.4%)	0.00	1.00	0.00
≥17	11 (0.0%)	1 (9.1%)	0.00	1.00	0.00
≥18	9 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥20	5 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥21	2 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥22	1 (0.0%)	0 (0.0%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 14: Tabular survival ROC results—opioid fill count/any substance use disorder

Opioid fill count cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
≥1	69668 (100.0%)	19713 (28.3%)	1.00	0.00	0.00
≥2*	35106 (50.4%)	12657 (36.1%)	0.62	0.56	0.42
≥3	19166 (27.5%)	8122 (42.4%)	0.39	0.79	0.35
≥4	9712 (13.9%)	4617 (47.5%)	0.22	0.90	0.21
≥5	5611 (8.1%)	2842 (50.7%)	0.13	0.95	0.13
≥6	3316 (4.8%)	1794 (54.1%)	0.08	0.97	0.08
≥7	1654 (2.4%)	926 (56.0%)	0.04	0.99	0.04
≥8	955 (1.4%)	547 (57.3%)	0.03	0.99	0.03
≥9	564 (0.8%)	337 (59.8%)	0.02	1.00	0.02
≥10	324 (0.5%)	204 (63.0%)	0.01	1.00	0.01
≥11	188 (0.3%)	123 (65.4%)	0.01	1.00	0.01
≥12	120 (0.2%)	76 (63.3%)	0.00	1.00	0.00
≥13	63 (0.1%)	47 (74.6%)	0.00	1.00	0.00
≥14	30 (0.0%)	23 (76.7%)	0.00	1.00	0.00
≥15	24 (0.0%)	20 (83.3%)	0.00	1.00	0.00
≥16	13 (0.0%)	10 (76.9%)	0.00	1.00	0.00
≥17	11 (0.0%)	8 (72.7%)	0.00	1.00	0.00
≥18	9 (0.0%)	6 (66.7%)	0.00	1.00	0.00
≥20	5 (0.0%)	3 (60.0%)	0.00	1.00	0.00
≥21	2 (0.0%)	1 (50.0%)	0.00	1.00	0.00
≥22	1 (0.0%)	1 (100.0%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 15: Tabular survival ROC results—pharmacy count/unintentional opioid overdose

Pharmacy count cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
≥1	69668 (100.0%)	202 (0.3%)	1.00	0.00	0.00
≥2*	11218 (16.1%)	57 (0.5%)	0.29	0.84	0.27
≥3	2274 (3.3%)	24 (1.1%)	0.12	0.97	0.12
≥4	575 (0.8%)	8 (1.4%)	0.04	0.99	0.04
≥5	156 (0.2%)	2 (1.3%)	0.01	1.00	0.01
≥6	52 (0.1%)	0 (0.0%)	0.00	1.00	0.00
≥7	22 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥8	10 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥9	4 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥11	3 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥16	1 (0.0%)	0 (0.0%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 16: Tabular survival ROC results—pharmacy count/unintentional acetaminophen overdose

Pharmacy count cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
≥1	69668 (100.0%)	82 (0.1%)	1.00	0.00	0.00
≥2*	11218 (16.1%)	18 (0.2%)	0.21	0.84	0.20
≥3	2274 (3.3%)	8 (0.4%)	0.10	0.97	0.10
≥4	575 (0.8%)	4 (0.7%)	0.04	0.99	0.04
≥5	156 (0.2%)	0 (0.0%)	0.00	1.00	0.00
≥6	52 (0.1%)	0 (0.0%)	0.00	1.00	0.00
≥7	22 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥8	10 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥9	4 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥11	3 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥16	1 (0.0%)	0 (0.0%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 17: Tabular survival ROC results—pharmacy count/unintentional overdose, any drug

Pharmacy count cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
≥1	69668 (100.0%)	1040 (1.5%)	1.00	0.00	0.00
≥2*	11218 (16.1%)	281 (2.5%)	0.27	0.84	0.26
≥3	2274 (3.3%)	84 (3.7%)	0.08	0.97	0.08
≥4	575 (0.8%)	25 (4.3%)	0.02	0.99	0.02
≥5	156 (0.2%)	7 (4.5%)	0.01	1.00	0.01
≥6	52 (0.1%)	2 (3.8%)	0.00	1.00	0.00
≥7	22 (0.0%)	1 (4.5%)	0.00	1.00	0.00
≥8	10 (0.0%)	1 (10.0%)	0.00	1.00	0.00
≥9	4 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥11	3 (0.0%)	0 (0.0%)	0.00	1.00	0.00
≥16	1 (0.0%)	0 (0.0%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 18: Tabular survival ROC results—pharmacy count/opioid use disorder

Pharmacy count cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
≥1	69668 (100.0%)	2284 (3.3%)	1.00	0.00	0.00
≥2*	11218 (16.1%)	825 (7.4%)	0.37	0.85	0.35
≥3	2274 (3.3%)	304 (13.4%)	0.13	0.97	0.13
≥4	575 (0.8%)	95 (16.5%)	0.04	0.99	0.04
≥5	156 (0.2%)	24 (15.4%)	0.01	1.00	0.01
≥6	52 (0.1%)	7 (13.5%)	0.00	1.00	0.00
≥7	22 (0.0%)	4 (18.2%)	0.00	1.00	0.00
≥8	10 (0.0%)	3 (30.0%)	0.00	1.00	0.00
≥9	4 (0.0%)	1 (25.0%)	0.00	1.00	0.00
≥11	3 (0.0%)	1 (33.3%)	0.00	1.00	0.00
≥16	1 (0.0%)	0 (0.0%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 19: Tabular survival ROC results—pharmacy count/any substance use disorder

Pharmacy count cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
≥1	69668 (100.0%)	19713 (28.3%)	1.00	0.00	0.00
≥2	11218 (16.1%)	4686 (41.8%)	0.23	0.88	0.22
≥3	2274 (3.3%)	1196 (52.6%)	0.06	0.98	0.06
≥4	575 (0.8%)	339 (59.0%)	0.02	1.00	0.02
≥5	156 (0.2%)	90 (57.7%)	0.00	1.00	0.00
≥6	52 (0.1%)	30 (57.7%)	0.00	1.00	0.00
≥7	22 (0.0%)	15 (68.2%)	0.00	1.00	0.00
≥8	10 (0.0%)	8 (80.0%)	0.00	1.00	0.00
≥9	4 (0.0%)	4 (100.0%)	0.00	1.00	0.00
≥11	3 (0.0%)	3 (100.0%)	0.00	1.00	0.00
≥16	1 (0.0%)	1 (100.0%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 20: Tabular survival ROC results—mean daily MME/unintentional opioid overdose

MME/day cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
>0	69668 (100.0%)	202 (0.3%)	1.00	0.00	0.00
≥5	35250 (50.6%)	155 (0.4%)	0.74	0.49	0.43
≥10*	23122 (33.2%)	132 (0.6%)	0.60	0.67	0.48
≥20	14950 (21.5%)	106 (0.7%)	0.47	0.79	0.43
≥30	11131 (16.0%)	87 (0.8%)	0.38	0.84	0.36
≥40	8426 (12.1%)	75 (0.9%)	0.33	0.88	0.32
≥60	5659 (8.1%)	60 (1.1%)	0.26	0.92	0.25
≥80	3897 (5.6%)	49 (1.3%)	0.21	0.94	0.21
≥100	2965 (4.3%)	43 (1.5%)	0.18	0.96	0.18
≥125	2399 (3.4%)	40 (1.7%)	0.17	0.97	0.17
≥150	1983 (2.8%)	35 (1.8%)	0.15	0.97	0.15
≥175	1703 (2.4%)	28 (1.6%)	0.12	0.98	0.12
≥200	1441 (2.1%)	22 (1.5%)	0.09	0.98	0.09
≥250	1061 (1.5%)	15 (1.4%)	0.06	0.98	0.06
≥300	818 (1.2%)	12 (1.5%)	0.05	0.99	0.05
≥400	482 (0.7%)	7 (1.5%)	0.03	0.99	0.03
≥500	273 (0.4%)	4 (1.5%)	0.02	1.00	0.02
≥1000	38 (0.1%)	1 (2.6%)	0.00	1.00	0.00
≥2000	5 (0.0%)	0 (0.0%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 21: Tabular survival ROC results—mean daily MME/unintentional acetaminophen overdose

MME/day cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
>0	69668 (100.0%)	82 (0.1%)	1.00	0.00	0.00
≥5*	35250 (50.6%)	47 (0.1%)	0.56	0.49	0.33
≥10	23122 (33.2%)	36 (0.2%)	0.41	0.67	0.32
≥20	14950 (21.5%)	27 (0.2%)	0.30	0.79	0.27
≥30	11131 (16.0%)	23 (0.2%)	0.25	0.84	0.23
≥40	8426 (12.1%)	21 (0.2%)	0.23	0.88	0.22
≥60	5659 (8.1%)	10 (0.2%)	0.11	0.92	0.10
≥80	3897 (5.6%)	8 (0.2%)	0.08	0.94	0.08
≥100	2965 (4.3%)	5 (0.2%)	0.05	0.96	0.05
≥125	2399 (3.4%)	5 (0.2%)	0.05	0.97	0.05
≥150	1983 (2.8%)	2 (0.1%)	0.02	0.97	0.02
≥175	1703 (2.4%)	1 (0.1%)	0.01	0.98	0.01
≥200	1441 (2.1%)	1 (0.1%)	0.01	0.98	0.01
≥250	1061 (1.5%)	0 (0.0%)	0.00	0.98	0.00
≥300	818 (1.2%)	0 (0.0%)	0.00	0.99	0.00
≥400	482 (0.7%)	0 (0.0%)	0.00	0.99	0.00
≥500	273 (0.4%)	0 (0.0%)	0.00	1.00	0.00
≥1000	38 (0.1%)	0 (0.0%)	0.00	1.00	0.00
≥2000	5 (0.0%)	0 (0.0%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 22: Tabular survival ROC results—mean daily MME/unintentional overdose, any drug

MME/day cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
>0	69668 (100.0%)	1040 (1.5%)	1.00	0.00	0.00
≥5	35250 (50.6%)	712 (2.0%)	0.66	0.50	0.39
≥10*	23122 (33.2%)	545 (2.4%)	0.49	0.67	0.39
≥20	14950 (21.5%)	413 (2.8%)	0.36	0.79	0.32
≥30	11131 (16.0%)	332 (3.0%)	0.29	0.84	0.27
≥40	8426 (12.1%)	272 (3.2%)	0.23	0.88	0.22
≥60	5659 (8.1%)	191 (3.4%)	0.16	0.92	0.16
≥80	3897 (5.6%)	150 (3.8%)	0.13	0.95	0.12
≥100	2965 (4.3%)	114 (3.8%)	0.10	0.96	0.09
≥125	2399 (3.4%)	98 (4.1%)	0.08	0.97	0.08
≥150	1983 (2.8%)	87 (4.4%)	0.07	0.97	0.07
≥175	1703 (2.4%)	75 (4.4%)	0.06	0.98	0.06
≥200	1441 (2.1%)	63 (4.4%)	0.05	0.98	0.05
≥250	1061 (1.5%)	44 (4.1%)	0.04	0.99	0.04
≥300	818 (1.2%)	33 (4.0%)	0.03	0.99	0.03
≥400	482 (0.7%)	17 (3.5%)	0.01	0.99	0.01
≥500	273 (0.4%)	11 (4.0%)	0.01	1.00	0.01
≥1000	38 (0.1%)	3 (7.9%)	0.00	1.00	0.00
≥2000	5 (0.0%)	0 (0.0%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 23: Tabular survival ROC results—mean daily MME/opioid use disorder

MME/day cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
>0	69668 (100.0%)	2284 (3.3%)	1.00	0.00	0.00
≥5	35250 (50.6%)	1634 (4.6%)	0.70	0.50	0.42
≥10*	23122 (33.2%)	1283 (5.5%)	0.54	0.68	0.43
≥20	14950 (21.5%)	1011 (6.8%)	0.41	0.79	0.38
≥30	11131 (16.0%)	822 (7.4%)	0.33	0.85	0.31
≥40	8426 (12.1%)	691 (8.2%)	0.28	0.89	0.27
≥60	5659 (8.1%)	504 (8.9%)	0.20	0.92	0.20
≥80	3897 (5.6%)	397 (10.2%)	0.16	0.95	0.16
≥100	2965 (4.3%)	334 (11.3%)	0.13	0.96	0.13
≥125	2399 (3.4%)	287 (12.0%)	0.11	0.97	0.11
≥150	1983 (2.8%)	256 (12.9%)	0.10	0.97	0.10
≥175	1703 (2.4%)	224 (13.2%)	0.09	0.98	0.09
≥200	1441 (2.1%)	194 (13.5%)	0.08	0.98	0.08
≥250	1061 (1.5%)	152 (14.3%)	0.06	0.99	0.06
≥300	818 (1.2%)	128 (15.6%)	0.05	0.99	0.05
≥400	482 (0.7%)	77 (16.0%)	0.03	0.99	0.03
≥500	273 (0.4%)	45 (16.5%)	0.02	1.00	0.02
≥1000	38 (0.1%)	8 (21.1%)	0.00	1.00	0.00
≥2000	5 (0.0%)	1 (20.0%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 24: Tabular survival ROC results—mean daily MME/any substance use disorder

MME/day cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
>0	69668 (100.0%)	19713 (28.3%)	1.00	0.00	0.00
≥5*	35250 (50.6%)	12117 (34.4%)	0.60	0.54	0.39
≥10	23122 (33.2%)	8965 (38.8%)	0.43	0.72	0.36
≥20	14950 (21.5%)	6353 (42.5%)	0.29	0.83	0.27
≥30	11131 (16.0%)	4871 (43.8%)	0.22	0.87	0.21
≥40	8426 (12.1%)	3770 (44.7%)	0.17	0.91	0.17
≥60	5659 (8.1%)	2604 (46.0%)	0.12	0.94	0.12
≥80	3897 (5.6%)	1838 (47.2%)	0.08	0.96	0.08
≥100	2965 (4.3%)	1415 (47.7%)	0.06	0.97	0.06
≥125	2399 (3.4%)	1157 (48.2%)	0.05	0.97	0.05
≥150	1983 (2.8%)	981 (49.5%)	0.04	0.98	0.04
≥175	1703 (2.4%)	838 (49.2%)	0.04	0.98	0.04
≥200	1441 (2.1%)	718 (49.8%)	0.03	0.99	0.03
≥250	1061 (1.5%)	546 (51.5%)	0.02	0.99	0.02
≥300	818 (1.2%)	421 (51.5%)	0.02	0.99	0.02
≥400	482 (0.7%)	252 (52.3%)	0.01	1.00	0.01
≥500	273 (0.4%)	141 (51.6%)	0.01	1.00	0.01
≥1000	38 (0.1%)	18 (47.4%)	0.00	1.00	0.00
≥2000	5 (0.0%)	2 (40.0%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 25: Tabular survival ROC results—mean daily APAP mg/unintentional opioid overdose

APAP mg/day cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
>0	69668 (100.0%)	202 (0.3%)	1.00	0.00	0.00
≥50	66009 (94.7%)	186 (0.3%)	0.93	0.05	0.05
≥100	60633 (87.0%)	172 (0.3%)	0.86	0.13	0.12
≥200	41178 (59.1%)	146 (0.4%)	0.71	0.41	0.34
≥300	30845 (44.3%)	132 (0.4%)	0.63	0.56	0.42
≥400*	24770 (35.6%)	122 (0.5%)	0.57	0.65	0.44
≥500	21327 (30.6%)	108 (0.5%)	0.50	0.69	0.41
≥600	18448 (26.5%)	103 (0.6%)	0.47	0.74	0.41
≥700	16065 (23.1%)	92 (0.6%)	0.41	0.77	0.37
≥800	14657 (21.0%)	87 (0.6%)	0.39	0.79	0.35
≥900	13574 (19.5%)	81 (0.6%)	0.36	0.81	0.33
≥1000	12133 (17.4%)	72 (0.6%)	0.32	0.83	0.30
≥1250	9931 (14.3%)	60 (0.6%)	0.27	0.86	0.25
≥1500	7760 (11.1%)	50 (0.6%)	0.22	0.89	0.21
≥1750	6121 (8.8%)	40 (0.7%)	0.18	0.91	0.17
≥2000	4555 (6.5%)	25 (0.5%)	0.11	0.93	0.11
≥2500	2883 (4.1%)	19 (0.7%)	0.08	0.96	0.08
≥3000	1649 (2.4%)	10 (0.6%)	0.04	0.98	0.04
≥3500	894 (1.3%)	5 (0.6%)	0.02	0.99	0.02
≥4000	376 (0.5%)	1 (0.3%)	0.00	0.99	0.00
≥5000	124 (0.2%)	1 (0.8%)	0.00	1.00	0.00
≥6000	35 (0.1%)	1 (2.9%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 26: Tabular survival ROC results—mean daily APAP mg/unintentional acetaminophen overdose

APAP mg/day cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
>0	69668 (100.0%)	82 (0.1%)	1.00	0.00	0.00
≥50	66009 (94.7%)	76 (0.1%)	0.93	0.05	0.05
≥100	60633 (87.0%)	70 (0.1%)	0.86	0.13	0.12
≥200	41178 (59.1%)	50 (0.1%)	0.60	0.41	0.29
≥300*	30845 (44.3%)	45 (0.1%)	0.53	0.56	0.36
≥400	24770 (35.6%)	35 (0.1%)	0.41	0.64	0.31
≥500	21327 (30.6%)	32 (0.2%)	0.36	0.69	0.29
≥600	18448 (26.5%)	28 (0.2%)	0.31	0.74	0.26
≥700	16065 (23.1%)	26 (0.2%)	0.29	0.77	0.25
≥800	14657 (21.0%)	24 (0.2%)	0.26	0.79	0.23
≥900	13574 (19.5%)	23 (0.2%)	0.25	0.81	0.23
≥1000	12133 (17.4%)	21 (0.2%)	0.23	0.83	0.21
≥1250	9931 (14.3%)	18 (0.2%)	0.19	0.86	0.18
≥1500	7760 (11.1%)	13 (0.2%)	0.14	0.89	0.13
≥1750	6121 (8.8%)	12 (0.2%)	0.13	0.91	0.12
≥2000	4555 (6.5%)	7 (0.2%)	0.08	0.93	0.07
≥2500	2883 (4.1%)	7 (0.2%)	0.07	0.96	0.07
≥3000	1649 (2.4%)	4 (0.2%)	0.04	0.98	0.04
≥3500	894 (1.3%)	1 (0.1%)	0.01	0.99	0.01
≥4000	376 (0.5%)	1 (0.3%)	0.01	0.99	0.01
≥5000	124 (0.2%)	0 (0.0%)	0.00	1.00	0.00
≥6000	35 (0.1%)	0 (0.0%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 27: Tabular survival ROC results—mean daily APAP mg/unintentional overdose, any drug

APAP mg/day cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
>0	69668 (100.0%)	1040 (1.5%)	1.00	0.00	0.00
≥50	66009 (94.7%)	955 (1.4%)	0.92	0.05	0.05
≥100	60633 (87.0%)	884 (1.5%)	0.85	0.13	0.12
≥200	41178 (59.1%)	726 (1.8%)	0.68	0.41	0.33
≥300*	30845 (44.3%)	609 (2.0%)	0.56	0.56	0.38
≥400	24770 (35.6%)	532 (2.1%)	0.48	0.65	0.37
≥500	21327 (30.6%)	464 (2.2%)	0.41	0.70	0.34
≥600	18448 (26.5%)	422 (2.3%)	0.37	0.74	0.32
≥700	16065 (23.1%)	392 (2.4%)	0.34	0.77	0.30
≥800	14657 (21.0%)	355 (2.4%)	0.31	0.79	0.28
≥900	13574 (19.5%)	332 (2.4%)	0.29	0.81	0.26
≥1000	12133 (17.4%)	304 (2.5%)	0.26	0.83	0.24
≥1250	9931 (14.3%)	262 (2.6%)	0.22	0.86	0.21
≥1500	7760 (11.1%)	206 (2.7%)	0.18	0.89	0.17
≥1750	6121 (8.8%)	164 (2.7%)	0.14	0.91	0.14
≥2000	4555 (6.5%)	120 (2.6%)	0.10	0.94	0.10
≥2500	2883 (4.1%)	83 (2.9%)	0.07	0.96	0.07
≥3000	1649 (2.4%)	51 (3.1%)	0.04	0.98	0.04
≥3500	894 (1.3%)	28 (3.1%)	0.02	0.99	0.02
≥4000	376 (0.5%)	12 (3.2%)	0.01	0.99	0.01
≥5000	124 (0.2%)	4 (3.2%)	0.00	1.00	0.00
≥6000	35 (0.1%)	4 (11.4%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 28: Tabular survival ROC results—mean daily APAP mg/opioid use disorder

APAP mg/day cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
>0	69668 (100.0%)	2284 (3.3%)	1.00	0.00	0.00
≥50	66009 (94.7%)	2048 (3.1%)	0.90	0.05	0.04
≥100	60633 (87.0%)	1915 (3.2%)	0.84	0.13	0.11
≥200	41178 (59.1%)	1540 (3.7%)	0.67	0.41	0.33
≥300	30845 (44.3%)	1342 (4.4%)	0.57	0.56	0.39
≥400*	24770 (35.6%)	1192 (4.8%)	0.50	0.65	0.39
≥500	21327 (30.6%)	1058 (5.0%)	0.44	0.70	0.37
≥600	18448 (26.5%)	964 (5.2%)	0.40	0.74	0.35
≥700	16065 (23.1%)	886 (5.5%)	0.37	0.78	0.33
≥800	14657 (21.0%)	814 (5.6%)	0.33	0.79	0.30
≥900	13574 (19.5%)	758 (5.6%)	0.31	0.81	0.28
≥1000	12133 (17.4%)	695 (5.7%)	0.28	0.83	0.26
≥1250	9931 (14.3%)	571 (5.7%)	0.23	0.86	0.22
≥1500	7760 (11.1%)	439 (5.7%)	0.18	0.89	0.17
≥1750	6121 (8.8%)	355 (5.8%)	0.14	0.91	0.14
≥2000	4555 (6.5%)	249 (5.5%)	0.10	0.94	0.10
≥2500	2883 (4.1%)	143 (5.0%)	0.06	0.96	0.06
≥3000	1649 (2.4%)	82 (5.0%)	0.03	0.98	0.03
≥3500	894 (1.3%)	43 (4.8%)	0.02	0.99	0.02
≥4000	376 (0.5%)	20 (5.3%)	0.01	0.99	0.01
≥5000	124 (0.2%)	8 (6.5%)	0.00	1.00	0.00
≥6000	35 (0.1%)	2 (5.7%)	0.00	1.00	0.00

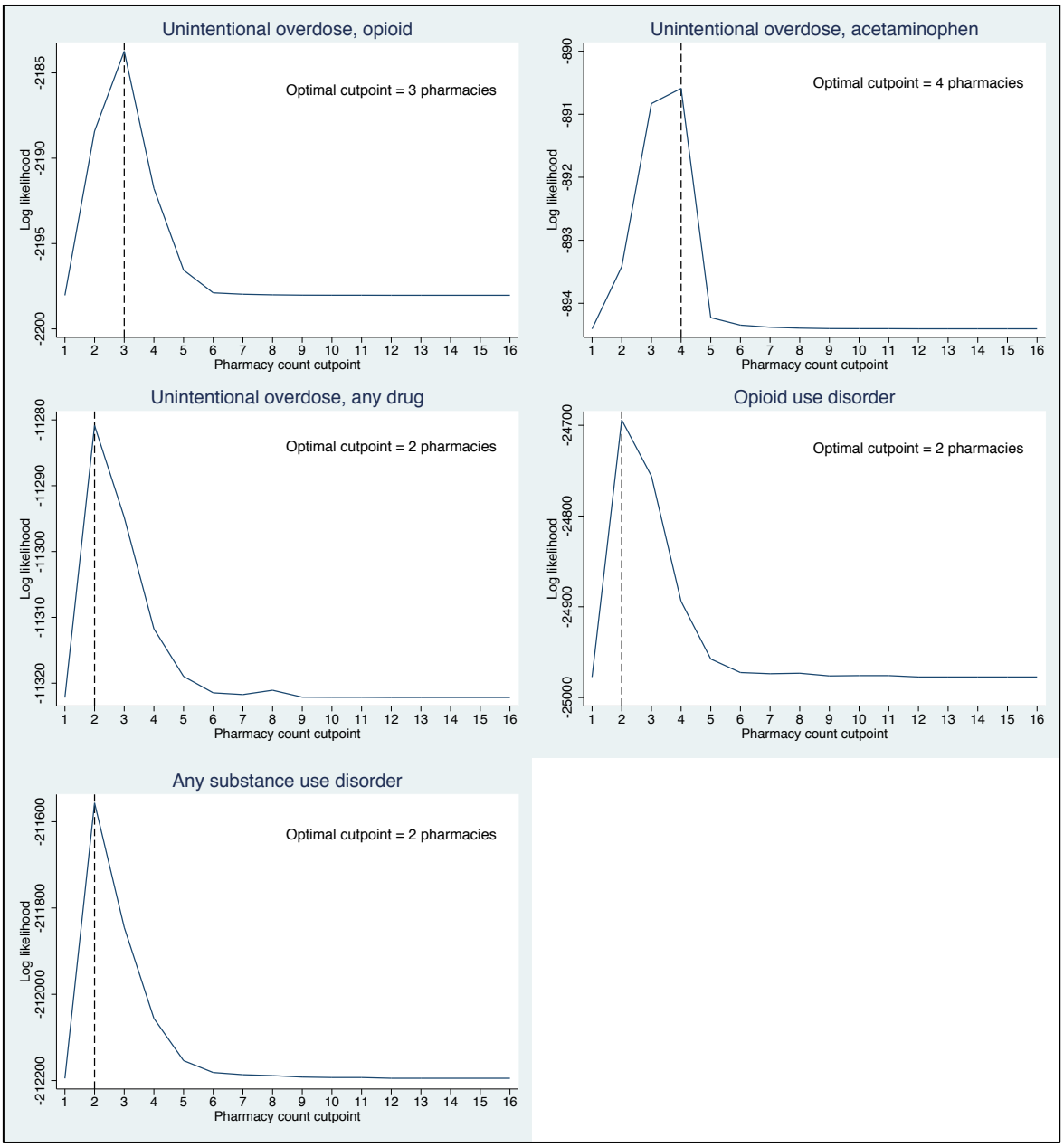
*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Table 29: Tabular survival ROC results—mean daily APAP mg/any substance use disorder

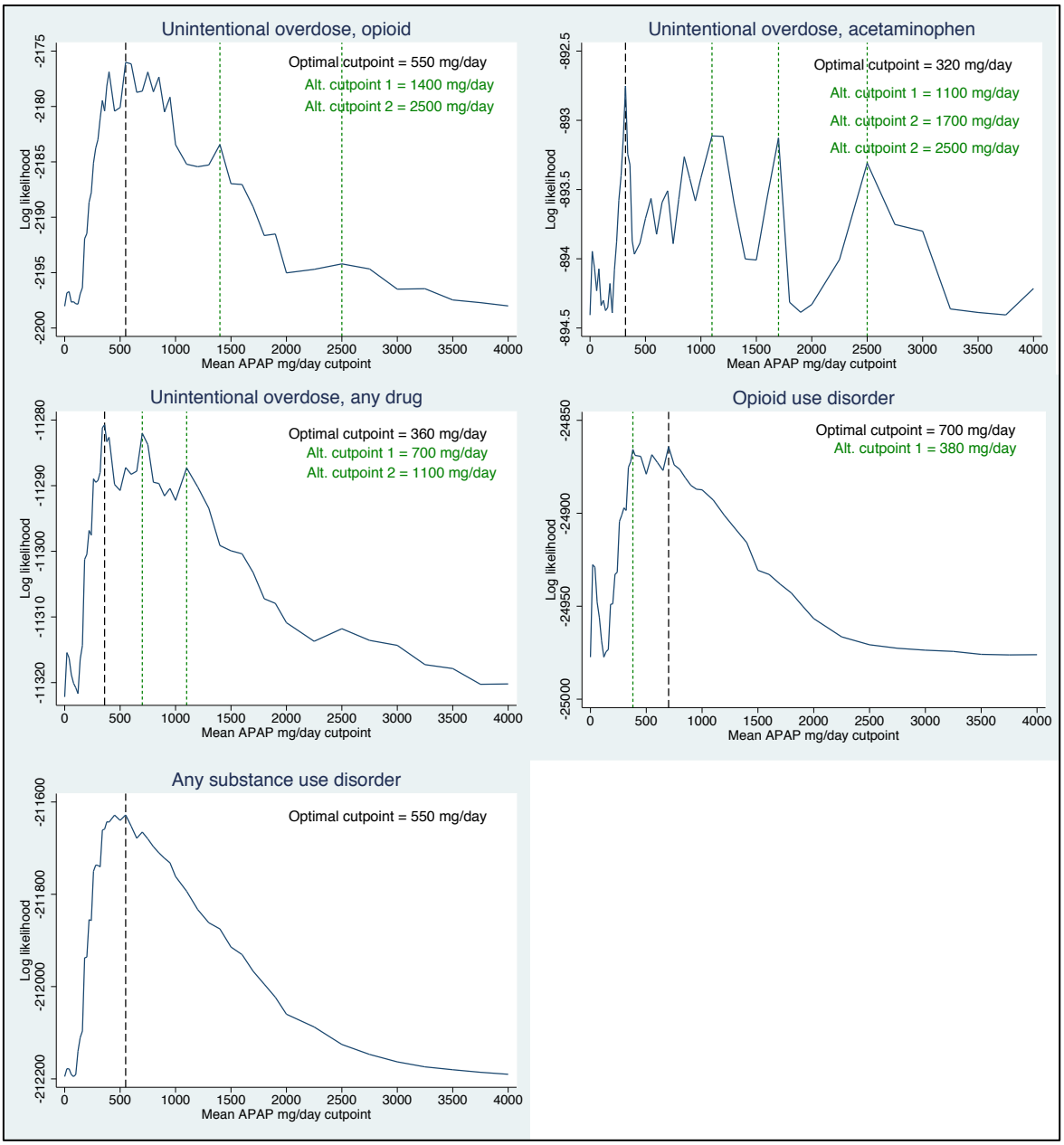
APAP mg/day cutpoint	Total subjects meeting cutpoint n (%)	Outcome events in cutpoint n (%)	Sensitivity	Specificity	Euclidean distance
>0	69668 (100.0%)	19713 (28.3%)	1.00	0.00	0.00
≥50	66009 (94.7%)	18493 (28.0%)	0.94	0.05	0.05
≥100	60633 (87.0%)	17222 (28.4%)	0.88	0.13	0.12
≥200	41178 (59.1%)	13072 (31.7%)	0.65	0.44	0.34
≥300*	30845 (44.3%)	10761 (34.9%)	0.52	0.60	0.38
≥400	24770 (35.6%)	9220 (37.2%)	0.44	0.69	0.36
≥500	21327 (30.6%)	8226 (38.6%)	0.39	0.74	0.34
≥600	18448 (26.5%)	7324 (39.7%)	0.34	0.78	0.31
≥700	16065 (23.1%)	6539 (40.7%)	0.31	0.81	0.28
≥800	14657 (21.0%)	6048 (41.3%)	0.28	0.83	0.26
≥900	13574 (19.5%)	5654 (41.7%)	0.26	0.84	0.24
≥1000	12133 (17.4%)	5103 (42.1%)	0.24	0.86	0.22
≥1250	9931 (14.3%)	4211 (42.4%)	0.19	0.88	0.18
≥1500	7760 (11.1%)	3349 (43.2%)	0.15	0.91	0.15
≥1750	6121 (8.8%)	2670 (43.6%)	0.12	0.93	0.12
≥2000	4555 (6.5%)	1944 (42.7%)	0.09	0.95	0.09
≥2500	2883 (4.1%)	1210 (42.0%)	0.05	0.97	0.05
≥3000	1649 (2.4%)	677 (41.1%)	0.03	0.98	0.03
≥3500	894 (1.3%)	362 (40.5%)	0.02	0.99	0.02
≥4000	376 (0.5%)	148 (39.4%)	0.01	1.00	0.01
≥5000	124 (0.2%)	44 (35.5%)	0.00	1.00	0.00
≥6000	35 (0.1%)	12 (34.3%)	0.00	1.00	0.00

*Optimal cutpoint based on joint maximized sensitivity/specificity

Appendix Figure 4: Distribution of log likelihood values from Cox proportional hazard models predicting Aim 3 outcomes at varied cutpoints of the pharmacy count measure



Appendix Figure 5: Distribution of log likelihood values from Cox proportional hazard models predicting Aim 3 outcomes at varied cutpoints of the mean APAP mg/day measure



Appendix Table 30: Describing application of selected opioid use criteria in Aim 3 validation sample for the secondary unintentional acetaminophen overdose outcome

	Criterion met (N=69,667)		Experienced outcome event* (N=90)			
	n	(% of total cohort)	n	(% within criterion)	Sens.Ŧ	Spec.Ŧ
Individual measures						
≥5 opioid fills	5525	(7.9%)	16	(0.3%)	0.176	0.921
≥12 MME/day	19926	(28.6%)	40	(0.2%)	0.413	0.714
≥45 MME/day	7541	(10.8%)	18	(0.2%)	0.176	0.892
≥140 MME/day	1980	(2.8%)	9	(0.5%)	0.087	0.972
NC MLIP standard: ≥7 opioid fills	1703	(2.4%)	5	(0.3%)	0.051	0.976
Combined criteria (unconditional)						
≥5 opioid fills or ≥12 MME/day	20404	(29.3%)	43	(0.2%)	0.445	0.707
≥5 opioid fills or ≥45 MME/day	10545	(15.1%)	27	(0.3%)	0.277	0.849
≥5 opioid fills or ≥140 MME/day	6336	(9.1%)	21	(0.3%)	0.227	0.909
≥7 opioid fills or ≥12 MME/day	19970	(28.7%)	40	(0.2%)	0.413	0.714
≥7 opioid fills or ≥45 MME/day	8370	(12.0%)	21	(0.3%)	0.208	0.880
≥7 opioid fills or ≥140 MME/day	3336	(4.8%)	12	(0.4%)	0.121	0.952
Combined measures (conditional)						
≥5 opioid fills and ≥12 MME/day	5047	(7.2%)	13	(0.3%)	0.142	0.928
≥5 opioid fills and ≥45 MME/day	2521	(3.6%)	7	(0.3%)	0.072	0.964
≥5 opioid fills and ≥140 MME/day	1169	(1.7%)	4	(0.3%)	0.039	0.983
≥7 opioid fills and ≥12 MME/day	1659	(2.4%)	5	(0.3%)	0.051	0.976
≥7 opioid fills and ≥45 MME/day	874	(1.3%)	2	(0.2%)	0.020	0.987
≥7 opioid fills and ≥140 MME/day	347	(0.5%)	2	(0.6%)	0.019	0.995

Note: Sens=Sensitivity; Spec=Specificity; MME=Milligram morphine equivalent; NC MLIP=North Carolina Medicaid lock-in program.
*Reported percentages in the "Experienced outcome event" column refer to the proportion of subjects flagged as high risk for that given opioid use criterion in that row.
Ŧ Reported sensitivities and specificities are time-dependent measures calculated at 365 days of follow-up using survival ROC models accounting for time to event. Interpretation of these figures should be per-person-year.

Appendix Table 31: Describing application of selected opioid use criteria in Aim 3 validation sample for the secondary outcome of an unintentional overdose of any drug

	Criterion met (N=69,667)		Experienced outcome event* (N=1,121)			
	n	(% of total cohort)	n	(% within criterion)	Sens.Ŧ	Spec.Ŧ
Individual measures						
≥5 opioid fills	5525	(7.9%)	214	(3.9%)	0.181	0.923
≥12 MME/day	19926	(28.6%)	549	(2.8%)	0.452	0.718
≥45 MME/day	7541	(10.8%)	256	(3.4%)	0.202	0.894
≥140 MME/day	1980	(2.8%)	91	(4.6%)	0.070	0.972
NC MLIP standard: ≥7 opioid fills	1703	(2.4%)	80	(4.7%)	0.067	0.976
Combined criteria (unconditional)						
≥5 opioid fills or ≥12 MME/day	20404	(29.3%)	566	(2.8%)	0.466	0.711
≥5 opioid fills or ≥45 MME/day	10545	(15.1%)	356	(3.4%)	0.290	0.852
≥5 opioid fills or ≥140 MME/day	6336	(9.1%)	255	(4.0%)	0.213	0.912
≥7 opioid fills or ≥12 MME/day	19970	(28.7%)	549	(2.7%)	0.452	0.717
≥7 opioid fills or ≥45 MME/day	8370	(12.0%)	282	(3.4%)	0.225	0.882
≥7 opioid fills or ≥140 MME/day	3336	(4.8%)	155	(4.6%)	0.125	0.954
Combined measures (conditional)						
≥5 opioid fills and ≥12 MME/day	5047	(7.2%)	197	(3.9%)	0.166	0.930
≥5 opioid fills and ≥45 MME/day	2521	(3.6%)	114	(4.5%)	0.091	0.965
≥5 opioid fills and ≥140 MME/day	1169	(1.7%)	50	(4.3%)	0.039	0.984
≥7 opioid fills and ≥12 MME/day	1659	(2.4%)	80	(4.8%)	0.067	0.977
≥7 opioid fills and ≥45 MME/day	874	(1.3%)	54	(6.2%)	0.043	0.988
≥7 opioid fills and ≥140 MME/day	347	(0.5%)	16	(4.6%)	0.012	0.995

Note: Sens=Sensitivity; Spec=Specificity; MME=Milligram morphine equivalent; NC MLIP=North Carolina Medicaid lock-in program.
*Reported percentages in the "Experienced outcome event" column refer to the proportion of subjects flagged as high risk for that given opioid use criterion in that row.
Ŧ Reported sensitivities and specificities are time-dependent measures calculated at 365 days of follow-up using survival ROC models accounting for time to event. Interpretation of these figures should be per-person-year.

Appendix Table 32: Describing application of selected opioid use criteria in Aim 3 validation sample for the secondary opioid use disorder outcome

	Criterion met (N=69,667)		Experienced outcome event* (N=2,241)			
	n	(% of total cohort)	n	(% within criterion)	Sens.Ŧ	Spec.Ŧ
Individual measures						
≥5 opioid fills	5525	(7.9%)	557	(10.1%)	0.243	0.928
≥12 MME/day	19926	(28.6%)	1142	(5.7%)	0.485	0.722
≥45 MME/day	7541	(10.8%)	606	(8.0%)	0.248	0.898
≥140 MME/day	1980	(2.8%)	243	(12.3%)	0.097	0.974
NC MLIP standard: ≥7 opioid fills	1703	(2.4%)	216	(12.7%)	0.094	0.978
Combined criteria (unconditional)						
≥5 opioid fills or ≥12 MME/day	20404	(29.3%)	1186	(5.8%)	0.504	0.716
≥5 opioid fills or ≥45 MME/day	10545	(15.1%)	856	(8.1%)	0.361	0.857
≥5 opioid fills or ≥140 MME/day	6336	(9.1%)	637	(10.1%)	0.275	0.917
≥7 opioid fills or ≥12 MME/day	19970	(28.7%)	1145	(5.7%)	0.486	0.722
≥7 opioid fills or ≥45 MME/day	8370	(12.0%)	694	(8.3%)	0.287	0.887
≥7 opioid fills or ≥140 MME/day	3336	(4.8%)	398	(11.9%)	0.166	0.957
Combined measures (conditional)						
≥5 opioid fills and ≥12 MME/day	5047	(7.2%)	513	(10.2%)	0.223	0.934
≥5 opioid fills and ≥45 MME/day	2521	(3.6%)	307	(12.2%)	0.127	0.968
≥5 opioid fills and ≥140 MME/day	1169	(1.7%)	163	(13.9%)	0.066	0.985
≥7 opioid fills and ≥12 MME/day	1659	(2.4%)	213	(12.8%)	0.092	0.979
≥7 opioid fills and ≥45 MME/day	874	(1.3%)	128	(14.6%)	0.053	0.989
≥7 opioid fills and ≥140 MME/day	347	(0.5%)	61	(17.6%)	0.024	0.996

Note: Sens=Sensitivity; Spec=Specificity; MME=Milligram morphine equivalent; NC MLIP=North Carolina Medicaid lock-in program.
*Reported percentages in the "Experienced outcome event" column refer to the proportion of subjects flagged as high risk for that given opioid use criterion in that row.
Ŧ Reported sensitivities and specificities are time-dependent measures calculated at 365 days of follow-up using survival ROC models accounting for time to event. Interpretation of these figures should be per-person-year.

Appendix Table 33: Describing application of selected opioid use criteria in Aim 3 validation sample for the secondary outcome of any substance use disorder

	Criterion met (N=69,667)		Experienced outcome event* (N=19,820)			
	n	(% of total cohort)	n	(% within criterion)	Sens.Ŧ	Spec.Ŧ
Individual measures						
≥5 opioid fills	5525	(7.9%)	2801	(50.7%)	0.132	0.950
≥12 MME/day	19926	(28.6%)	7930	(39.8%)	0.371	0.760
≥45 MME/day	7541	(10.8%)	3293	(43.7%)	0.149	0.914
≥140 MME/day	1980	(2.8%)	956	(48.3%)	0.043	0.979
NC MLIP standard: ≥7 opioid fills	1703	(2.4%)	981	(57.6%)	0.046	0.987
Combined criteria (unconditional)						
≥5 opioid fills or ≥12 MME/day	20404	(29.3%)	8177	(40.1%)	0.383	0.756
≥5 opioid fills or ≥45 MME/day	10545	(15.1%)	4801	(45.5%)	0.222	0.887
≥5 opioid fills or ≥140 MME/day	6336	(9.1%)	3156	(49.8%)	0.148	0.940
≥7 opioid fills or ≥12 MME/day	19970	(28.7%)	7958	(39.8%)	0.372	0.760
≥7 opioid fills or ≥45 MME/day	8370	(12.0%)	3763	(45.0%)	0.171	0.908
≥7 opioid fills or ≥140 MME/day	3336	(4.8%)	1734	(52.0%)	0.079	0.969
Combined measures (conditional)						
≥5 opioid fills and ≥12 MME/day	5047	(7.2%)	2554	(50.6%)	0.120	0.954
≥5 opioid fills and ≥45 MME/day	2521	(3.6%)	1293	(51.3%)	0.059	0.976
≥5 opioid fills and ≥140 MME/day	1169	(1.7%)	601	(51.4%)	0.027	0.989
≥7 opioid fills and ≥12 MME/day	1659	(2.4%)	953	(57.4%)	0.044	0.987
≥7 opioid fills and ≥45 MME/day	874	(1.3%)	511	(58.5%)	0.023	0.993
≥7 opioid fills and ≥140 MME/day	347	(0.5%)	203	(58.5%)	0.009	0.997

Note: Sens=Sensitivity; Spec=Specificity; MME=Milligram morphine equivalent; NC MLIP=North Carolina Medicaid lock-in program.
*Reported percentages in the "Experienced outcome event" column refer to the proportion of subjects flagged as high risk for that given opioid use criterion in that row.
Ŧ Reported sensitivities and specificities are time-dependent measures calculated at 365 days of follow-up using survival ROC models accounting for time to event. Interpretation of these figures should be per-person-year.

Appendix Table 34: Bivariate Cox proportional hazard model results estimating the hazard of an unintentional acetaminophen overdose for each opioid use criterion

	Criterion met (N=69,667)			
	n (%)	**Hazard ratio**	**95% CI**	**LL**
Individual measures				
≥5 opioid fills	5525 (7.9%)	2.39**	(1.39 , 4.10)	-975.6
≥12 MME/day	19926 (28.6%)	1.78**	(1.17 , 2.69)	-976.2
≥45 MME/day	7541 (10.8%)	1.79*	(1.07 , 3.00)	-977.5
≥140 MME/day	1980 (2.8%)	3.27***	(1.64 , 6.50)	-975.5
NC MLIP standard: ≥7 opioid fills	1703 (2.4%)	2.21	(0.90 , 5.46)	-978.5
Combined criteria (unconditional)				
≥5 opioid fills or ≥12 MME/day	20404 (29.3%)	1.97***	(1.30 , 2.98)	-974.7
≥5 opioid fills or ≥45 MME/day	10545 (15.1%)	2.17***	(1.38 , 3.40)	-974.7
≥5 opioid fills or ≥140 MME/day	6336 (9.1%)	2.84***	(1.75 , 4.64)	-972.5
≥7 opioid fills or ≥12 MME/day	19970 (28.7%)	1.77**	(1.17 , 2.68)	-976.2
≥7 opioid fills or ≥45 MME/day	8370 (12.0%)	1.96**	(1.20 , 3.19)	-976.5
≥7 opioid fills or ≥140 MME/day	3336 (4.8%)	2.75***	(1.50 , 5.05)	-975.5
Combined measures (conditional)				
≥5 opioid fills and ≥12 MME/day	5047 (7.2%)	2.04*	(1.13 , 3.67)	-1865.6
≥5 opioid fills and ≥45 MME/day	2521 (3.6%)	2.00	(0.92 , 4.32)	-1863.6
≥5 opioid fills and ≥140 MME/day	1169 (1.7%)	2.36	(0.86 , 6.42)	-1874.5
≥7 opioid fills and ≥12 MME/day	1659 (2.4%)	2.27	(0.92 , 5.59)	-1881.2
≥7 opioid fills and ≥45 MME/day	874 (1.3%)	1.59	(0.39 , 6.47)	-1877.4
≥7 opioid fills and ≥140 MME/day	347 (0.5%)	3.89	(0.96 , 15.82)	-1883.1

Note: CI=Confidence interval; LL=Log likelihood; MME=Milligram morphine equivalent; NC MLIP=North Carolina Medicaid lock-in program. All hazard ratio estimates reported in this table were statistically significant at p<0.001. *p<0.05; **p<0.01; ***p<0.001

Appendix Table 35: Bivariate Cox proportional hazard model results estimating the hazard of any overdose event for each opioid use criterion

	Criterion met (N=69,667)			
	n (%)	Hazard ratio	95% CI	LL
Individual measures				
≥5 opioid fills	5525 (7.9%)	2.64	(2.28 , 3.07)	-12127.9
≥12 MME/day	19926 (28.6%)	2.15	(1.91 , 2.41)	-12114.7
≥45 MME/day	7541 (10.8%)	2.14	(1.86 , 2.46)	-12144.9
≥140 MME/day	1980 (2.8%)	2.64	(2.13 , 3.27)	-12163.9
NC MLIP standard: ≥7 opioid fills	1703 (2.4%)	2.95	(2.35 , 3.70)	-12161.9
Combined criteria (unconditional)				
≥5 opioid fills or ≥12 MME/day	20404 (29.3%)	2.21	(1.97 , 2.49)	-12107.8
≥5 opioid fills or ≥45 MME/day	10545 (15.1%)	2.38	(2.10 , 2.70)	-12113.8
≥5 opioid fills or ≥140 MME/day	6336 (9.1%)	2.79	(2.43 , 3.21)	-12109.2
≥7 opioid fills or ≥12 MME/day	19970 (28.7%)	2.14	(1.90 , 2.41)	-12115.3
≥7 opioid fills or ≥45 MME/day	8370 (12.0%)	2.19	(1.91 , 2.50)	-12138.1
≥7 opioid fills or ≥140 MME/day	3336 (4.8%)	2.92	(2.46 , 3.46)	-12135.0
Combined measures (conditional)				
≥5 opioid fills and ≥12 MME/day	5047 (7.2%)	2.61	(2.24 , 3.04)	-12133.8
≥5 opioid fills and ≥45 MME/day	2521 (3.6%)	2.73	(2.25 , 3.31)	-12154.4
≥5 opioid fills and ≥140 MME/day	1169 (1.7%)	2.40	(1.81 , 3.19)	-12180.0
≥7 opioid fills and ≥12 MME/day	1659 (2.4%)	3.02	(2.41 , 3.79)	-12160.6
≥7 opioid fills and ≥45 MME/day	874 (1.3%)	3.64	(2.77 , 4.79)	-12164.3
≥7 opioid fills and ≥140 MME/day	347 (0.5%)	2.52	(1.54 , 4.12)	-12189.1

Note: CI=Confidence interval; LL=Log likelihood; MME=Milligram morphine equivalent; NC MLIP=North Carolina Medicaid lock-in program. All hazard ratio estimates reported in this table were statistically significant at $p<0.001$.

Appendix Table 36: Bivariate Cox proportional hazard model results estimating the hazard of an opioid use disorder diagnosis for each opioid use criterion

	Criterion met (N=69,667)			
	n (%)	Hazard ratio	95% CI	LL
Individual measures				
≥5 opioid fills	5525 (7.9%)	3.83	(3.48 , 4.22)	-24198.8
≥12 MME/day	19926 (28.6%)	2.40	(2.21 , 2.61)	-24282.8
≥45 MME/day	7541 (10.8%)	2.80	(2.55 , 3.07)	-24296.4
≥140 MME/day	1980 (2.8%)	3.85	(3.37 , 4.40)	-24352.1
NC MLIP standard: ≥7 opioid fills	1703 (2.4%)	4.28	(3.72 , 4.92)	-24350.2
Combined criteria (unconditional)				
≥5 opioid fills or ≥12 MME/day	20404 (29.3%)	2.52	(2.32 , 2.74)	-24257.8
≥5 opioid fills or ≥45 MME/day	10545 (15.1%)	3.28	(3.01 , 3.57)	-24166.9
≥5 opioid fills or ≥140 MME/day	6336 (9.1%)	3.91	(3.57 , 4.28)	-24156.4
≥7 opioid fills or ≥12 MME/day	19970 (28.7%)	2.41	(2.22 , 2.62)	-24281.5
≥7 opioid fills or ≥45 MME/day	8370 (12.0%)	3.05	(2.79 , 3.33)	-24241.8
≥7 opioid fills or ≥140 MME/day	3336 (4.8%)	4.13	(3.70 , 4.60)	-24251.8
Combined measures (conditional)				
≥5 opioid fills and ≥12 MME/day	5047 (7.2%)	3.77	(3.41 , 4.16)	-24224.3
≥5 opioid fills and ≥45 MME/day	2521 (3.6%)	4.03	(3.57 , 4.54)	-24307.9
≥5 opioid fills and ≥140 MME/day	1169 (1.7%)	4.31	(3.68 , 5.06)	-24382.8
≥7 opioid fills and ≥12 MME/day	1659 (2.4%)	4.32	(3.75 , 4.97)	-24350.6
≥7 opioid fills and ≥45 MME/day	874 (1.3%)	4.62	(3.86 , 5.52)	-24398.9
≥7 opioid fills and ≥140 MME/day	347 (0.5%)	5.30	(4.11 , 6.84)	-24440.5

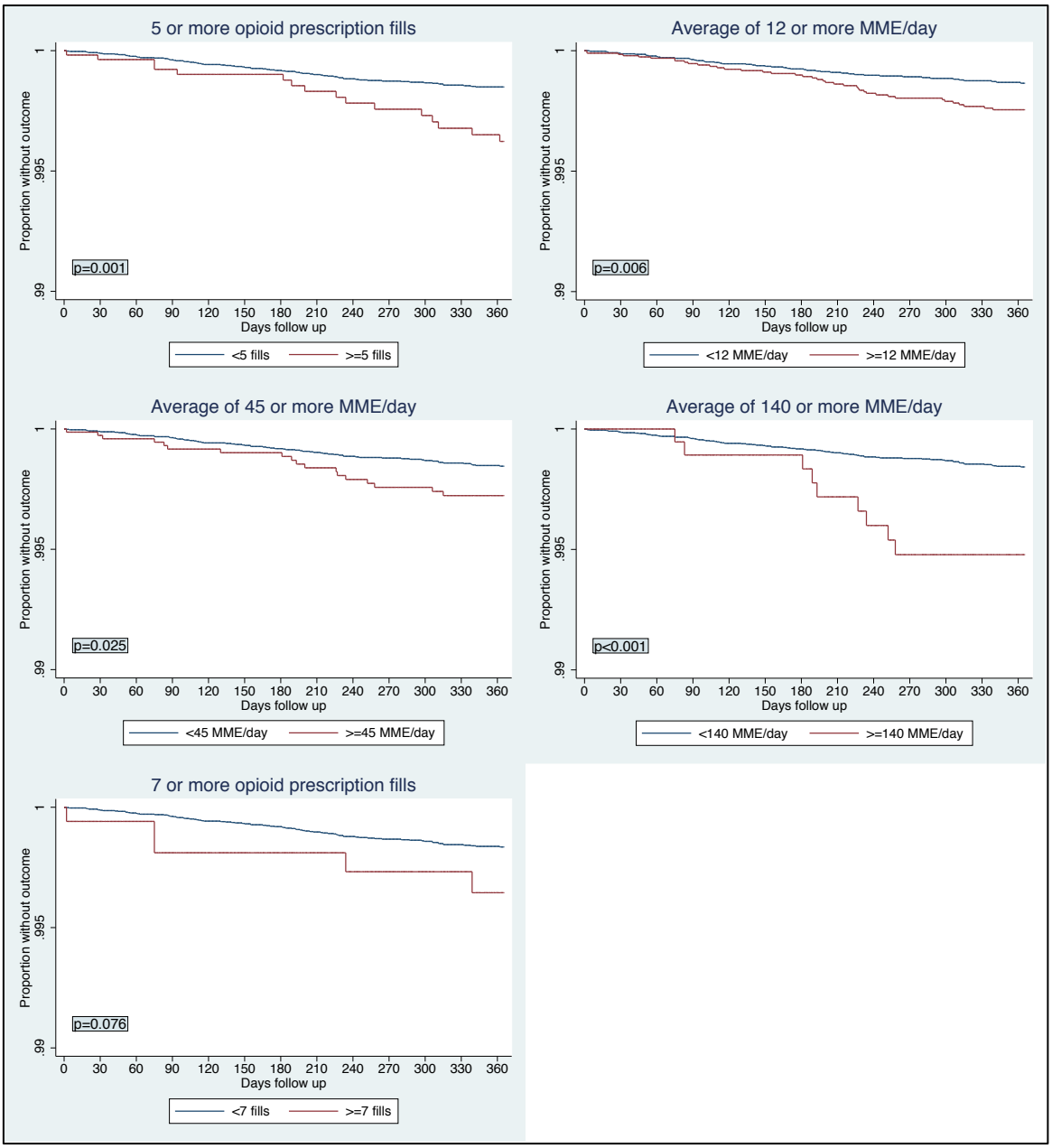
Note: CI=Confidence interval; LL=Log likelihood; MME=Milligram morphine equivalent; NC MLIP=North Carolina Medicaid lock-in program. All hazard ratio estimates reported in this table were statistically significant at $p<0.001$.

Appendix Table 37: Bivariate Cox proportional hazard model results estimating the hazard of any substance use disorder diagnosis for each opioid use criterion

	Criterion met (N=69,667)			
	n (%)	**Hazard ratio**	**95% CI**	**LL**
Individual measures				
≥5 opioid fills	5525 (7.9%)	2.27	(2.18 , 2.36)	-212631.5
≥12 MME/day	19926 (28.6%)	1.68	(1.63 , 1.73)	-212680.0
≥45 MME/day	7541 (10.8%)	1.63	(1.57 , 1.69)	-213002.0
≥140 MME/day	1980 (2.8%)	1.73	(1.63 , 1.85)	-213175.2
NC MLIP standard: ≥7 opioid fills	1703 (2.4%)	2.60	(2.44 , 2.77)	-212968.8
Combined criteria (unconditional)				
≥5 opioid fills or ≥12 MME/day	20404 (29.3%)	1.72	(1.68 , 1.77)	-212610.5
≥5 opioid fills or ≥45 MME/day	10545 (15.1%)	1.91	(1.85 , 1.97)	-212619.8
≥5 opioid fills or ≥140 MME/day	6336 (9.1%)	2.18	(2.10 , 2.27)	-212619.3
≥7 opioid fills or ≥12 MME/day	19970 (28.7%)	1.69	(1.64 , 1.73)	-212670.5
≥7 opioid fills or ≥45 MME/day	8370 (12.0%)	1.75	(1.69 , 1.81)	-212868.0
≥7 opioid fills or ≥140 MME/day	3336 (4.8%)	2.11	(2.01 , 2.22)	-212932.0
Combined measures (conditional)				
≥5 opioid fills and ≥12 MME/day	5047 (7.2%)	2.22	(2.13 , 2.32)	-212709.6
≥5 opioid fills and ≥45 MME/day	2521 (3.6%)	2.03	(1.91 , 2.14)	-213045.8
≥5 opioid fills and ≥140 MME/day	1169 (1.7%)	1.90	(1.75 , 2.06)	-213193.5
≥7 opioid fills and ≥12 MME/day	1659 (2.4%)	2.58	(2.42 , 2.75)	-212981.8
≥7 opioid fills and ≥45 MME/day	874 (1.3%)	2.43	(2.22 , 2.65)	-213142.3
≥7 opioid fills and ≥140 MME/day	347 (0.5%)	2.25	(1.96 , 2.59)	-213240.8

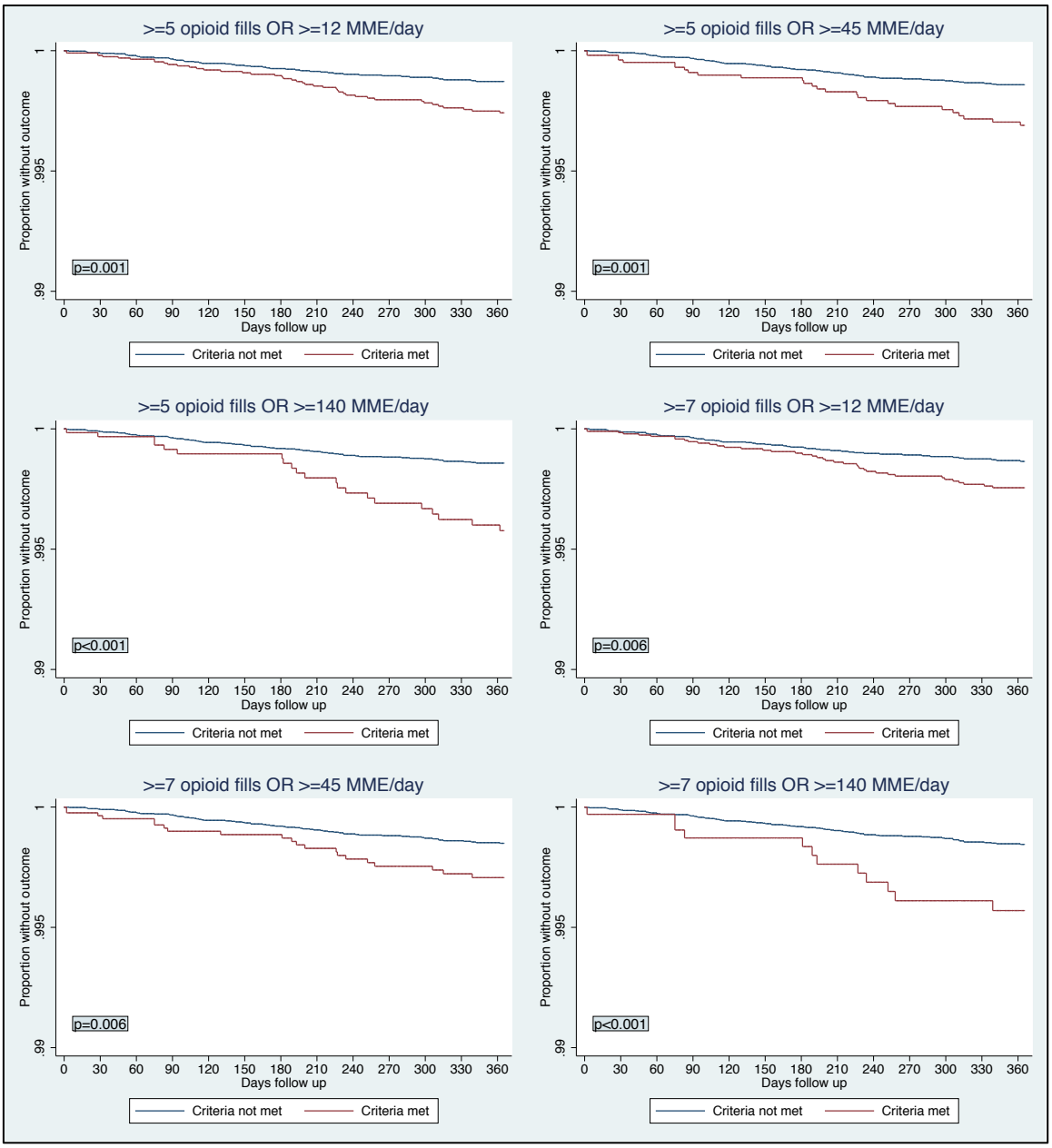
Note: CI=Confidence interval; LL=Log likelihood; MME=Milligram morphine equivalent; NC MLIP=North Carolina Medicaid lock-in program. All hazard ratio estimates reported in this table were statistically significant at $p<0.001$.

Appendix Figure 6: Kaplan-Meier survival function plots of time to an unintentional acetaminophen overdose event, by individual high risk opioid use measure criteria



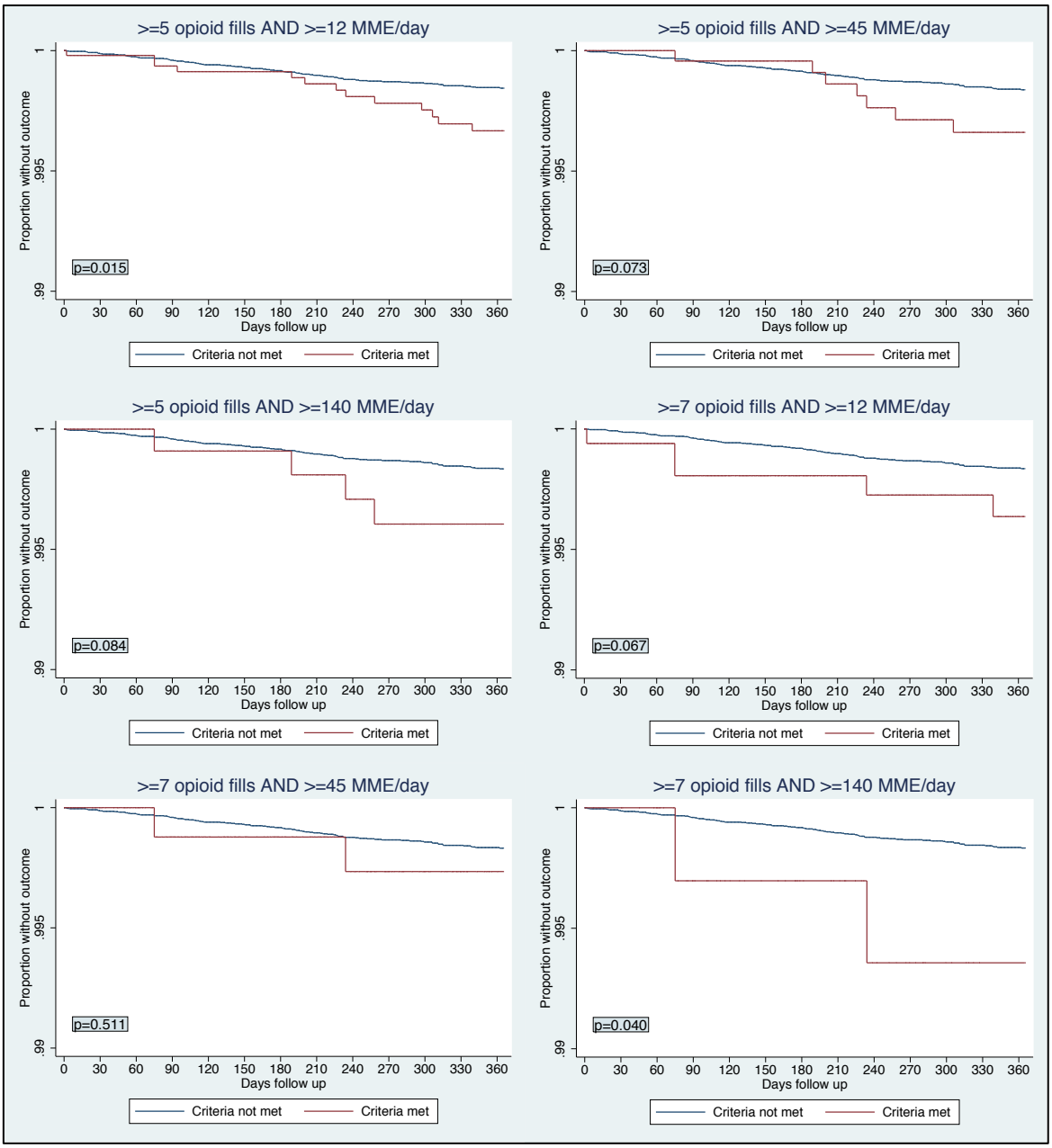
Note: p-values refer to a statistical test for the hypothesis that the survivor functions are equal

Appendix Figure 7: Kaplan-Meier survival function plots of time to an unintentional acetaminophen overdose event, by unconditional combination high risk opioid use measure criteria



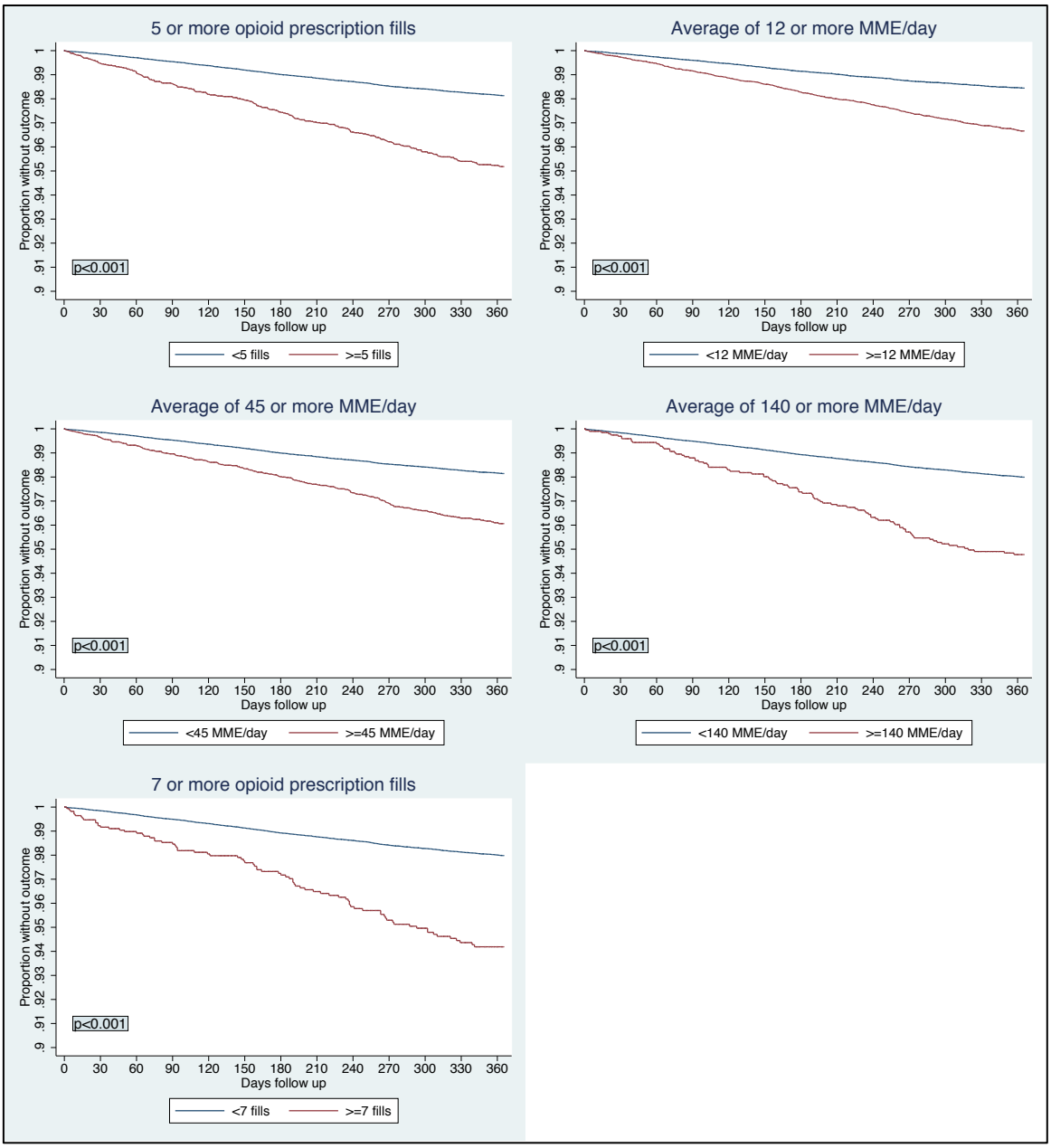
Note: p-values refer to a statistical test for the hypothesis that the survivor functions are equal

Appendix Figure 8: Kaplan-Meier survival function plots of time to an unintentional acetaminophen overdose event, by conditional combination high risk opioid use measure criteria



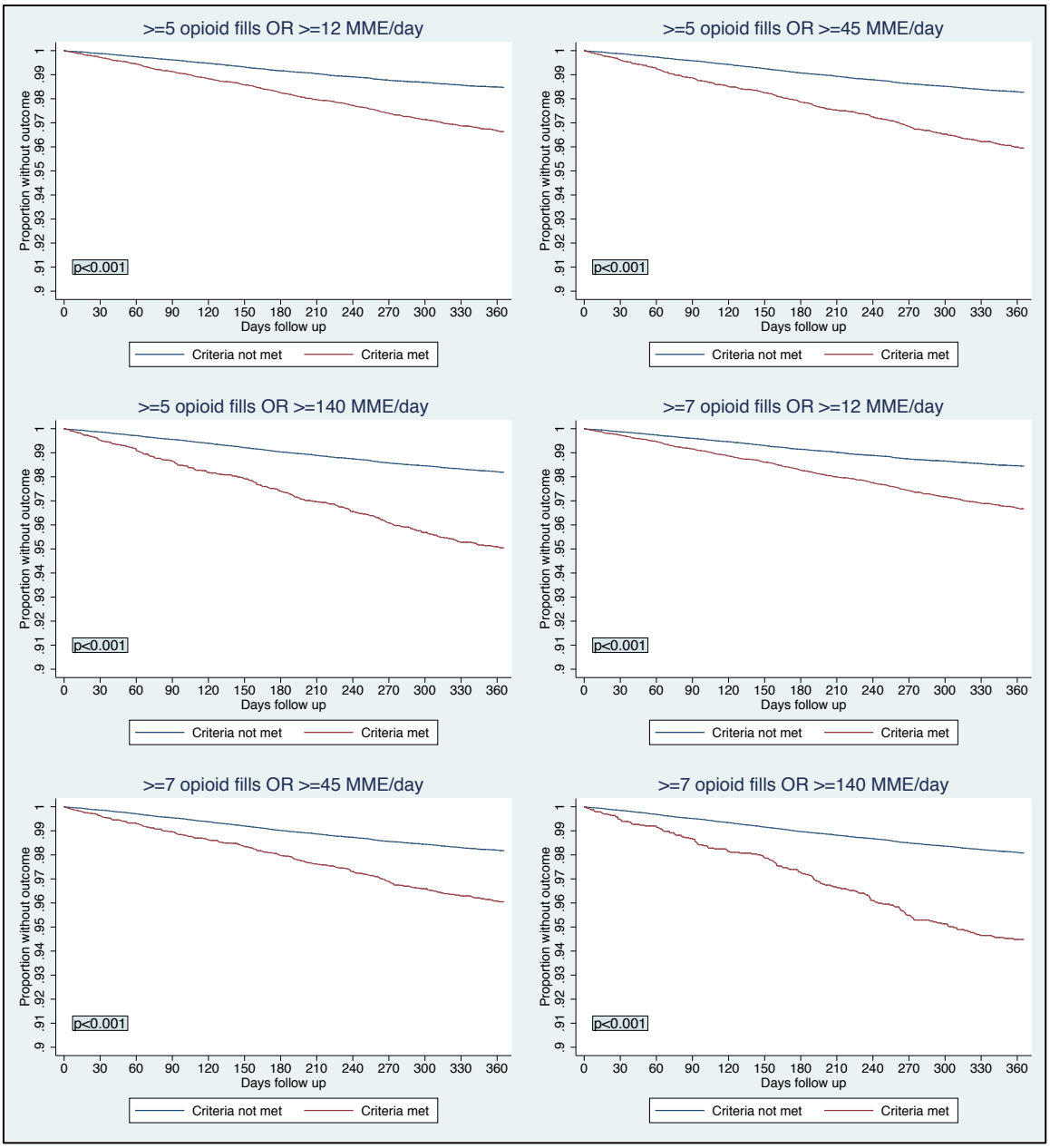
Note: p-values refer to a statistical test for the hypothesis that the survivor functions are equal

Appendix Figure 9: Kaplan-Meier survival function plots of time to any unintentional overdose event, by individual high risk opioid use measure criteria



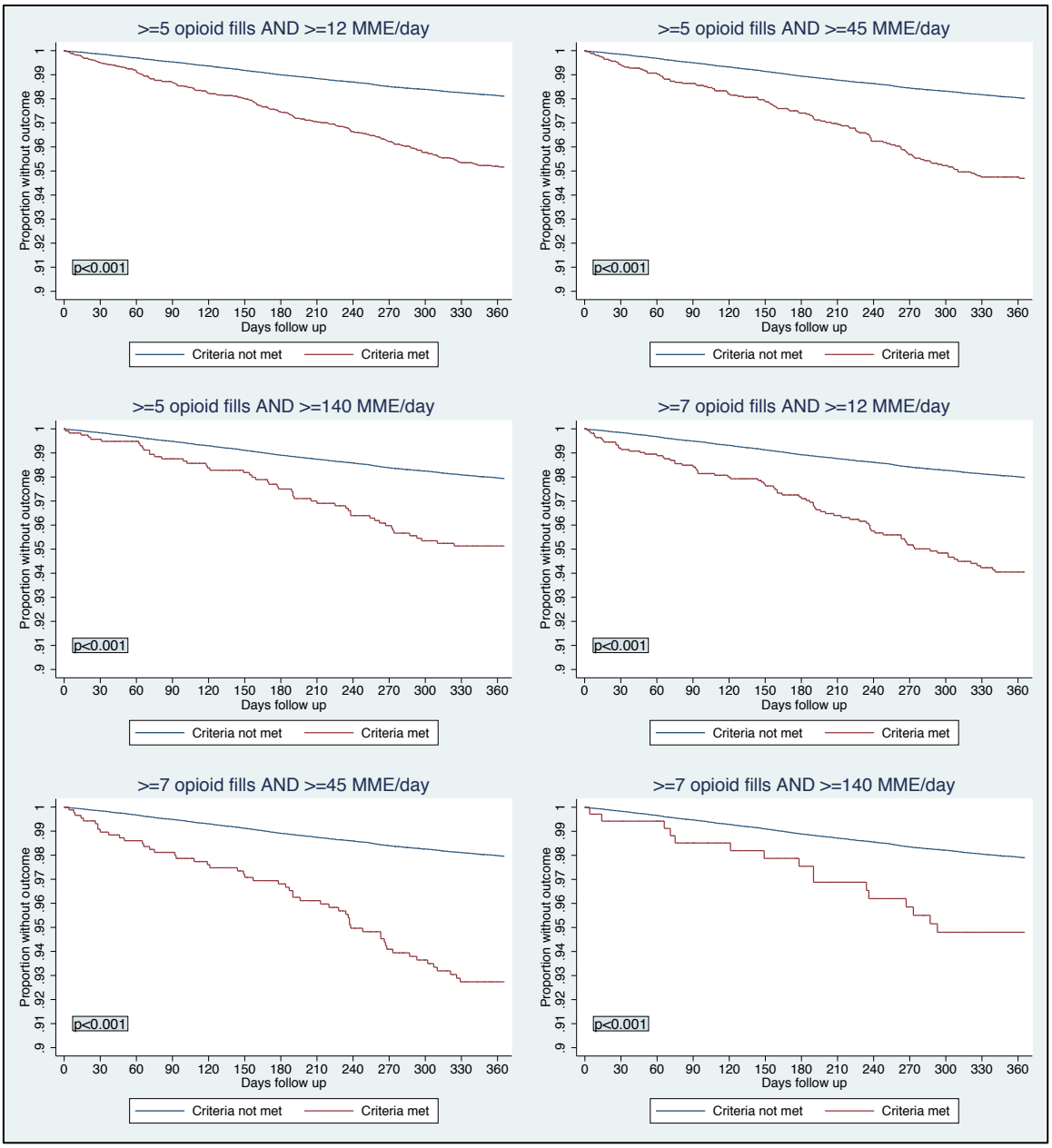
Note: p-values refer to a statistical test for the hypothesis that the survivor functions are equal

Appendix Figure 10: Kaplan-Meier survival function plots of time to any unintentional overdose event, by unconditional combined high risk opioid use measure criteria



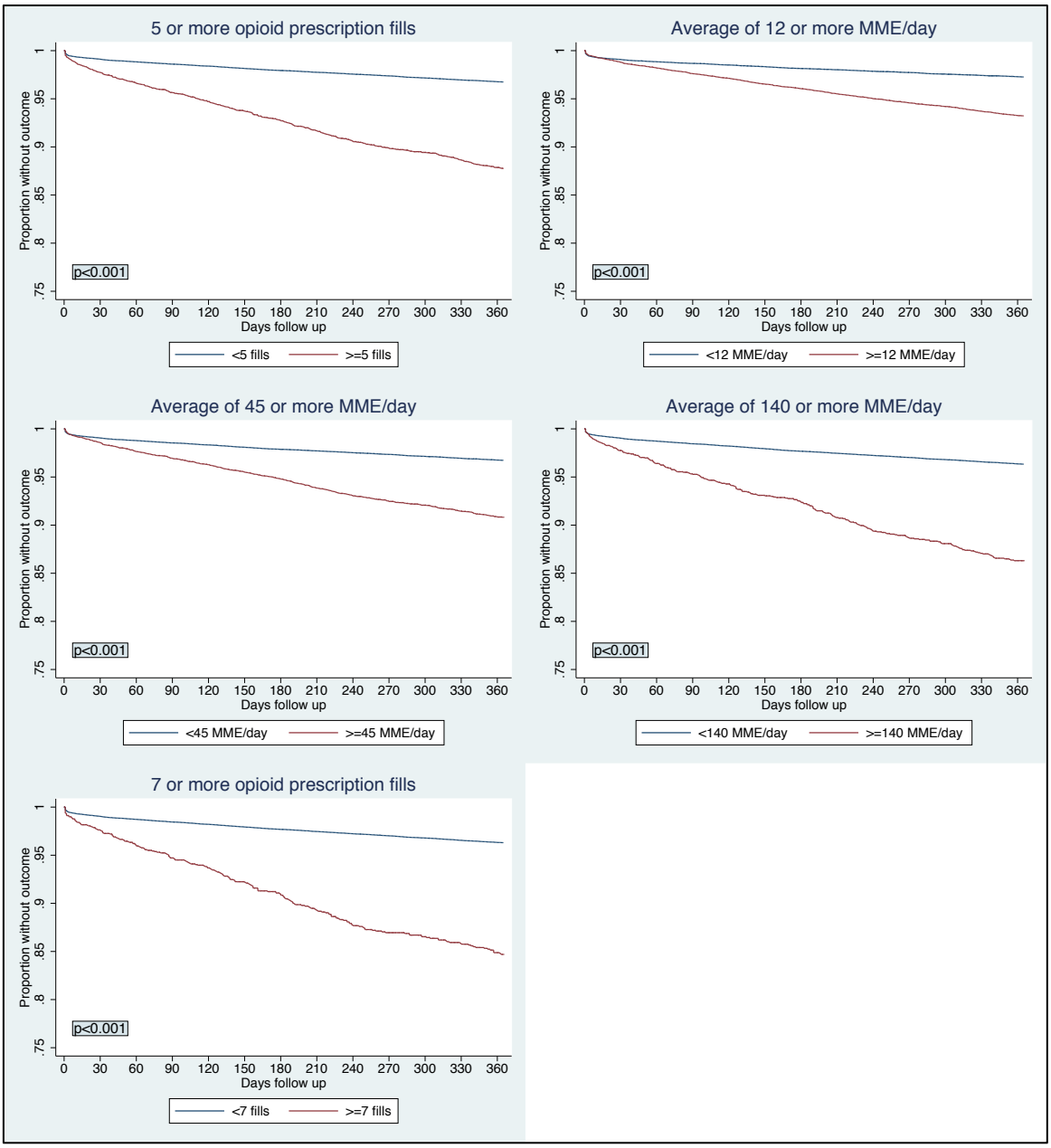
Note: p-values refer to a statistical test for the hypothesis that the survivor functions are equal

Appendix Figure 11: Kaplan-Meier survival function plots of time to any unintentional overdose event, by conditional combined high risk opioid use measure criteria



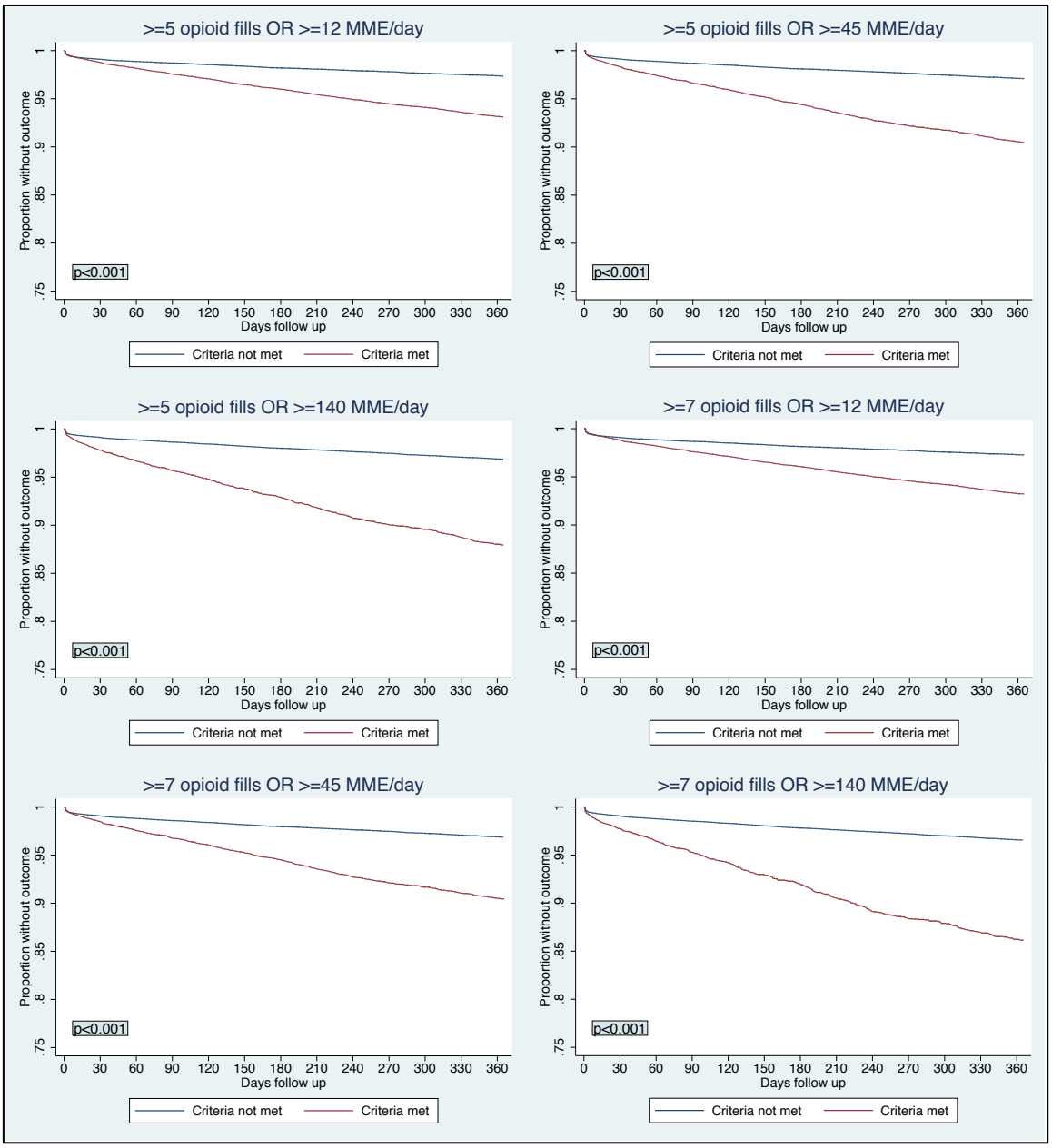
Note: p-values refer to a statistical test for the hypothesis that the survivor functions are equal

Appendix Figure 12: Kaplan-Meier survival function plots of time to an opioid use disorder diagnosis, by individual high risk opioid use measure criteria



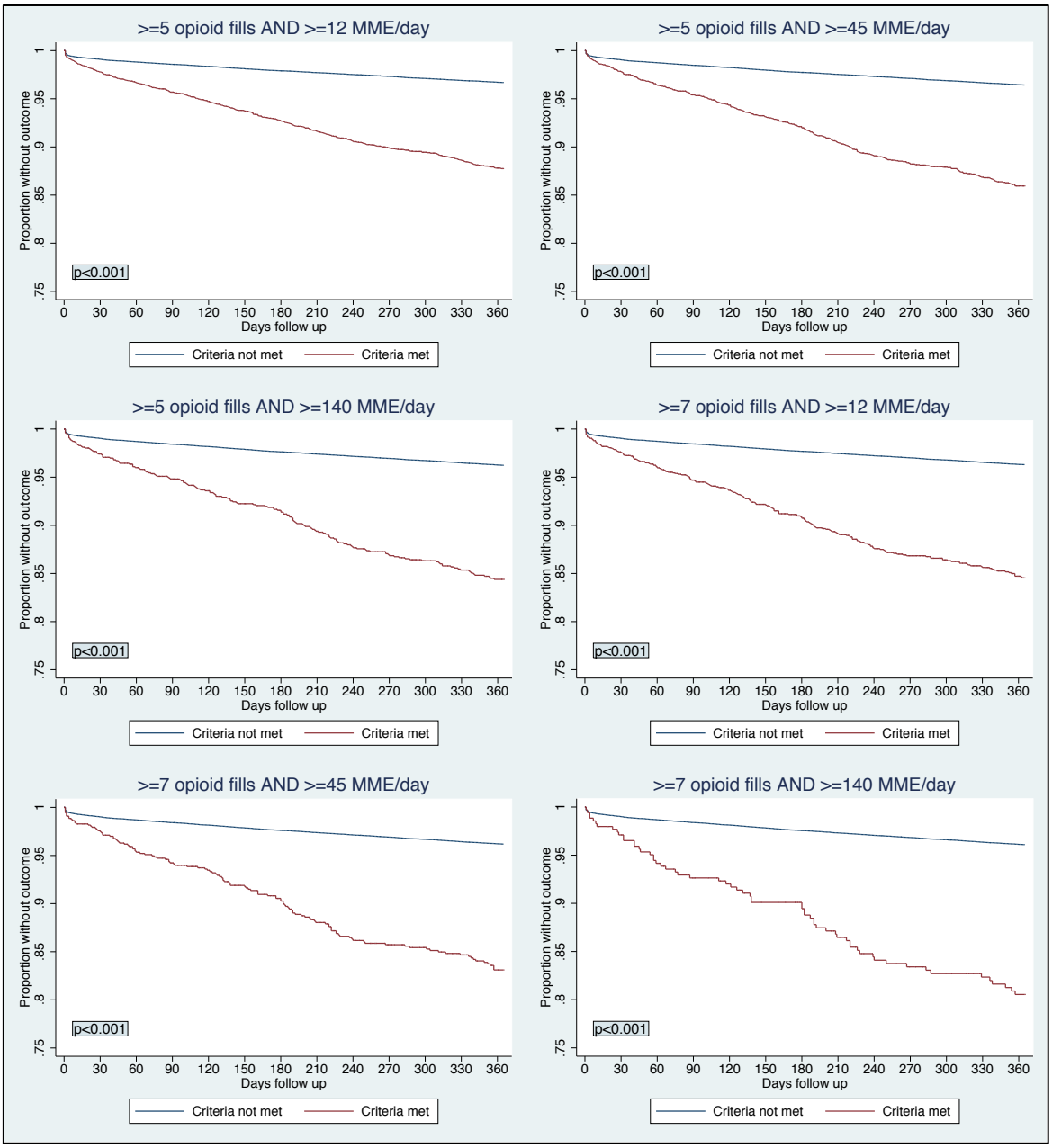
Note: p-values refer to a statistical test for the hypothesis that the survivor functions are equal

Appendix Figure 13: Kaplan-Meier survival function plots of time to an opioid use disorder diagnosis, by unconditional combined high risk opioid use measure criteria



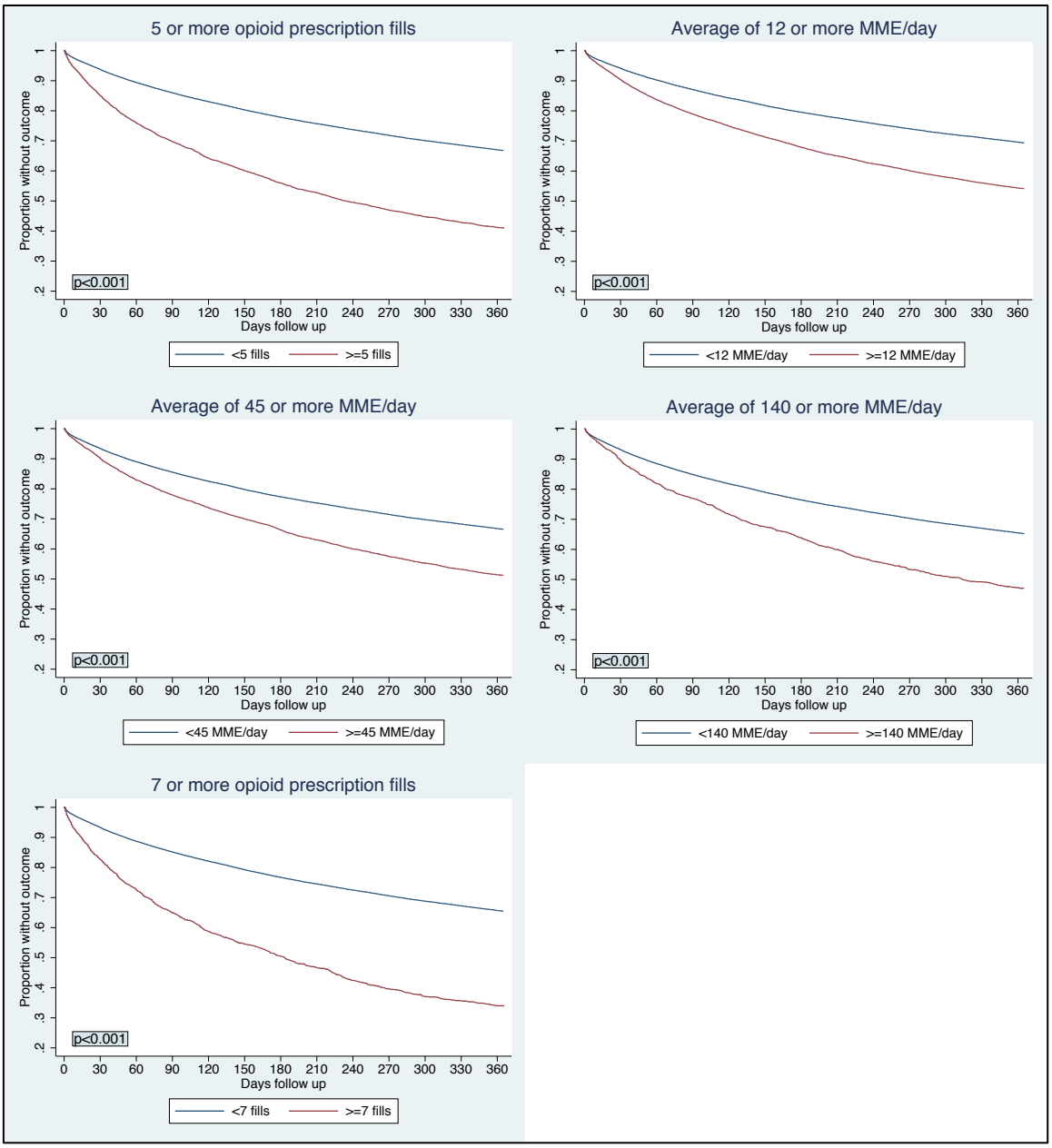
Note: p-values refer to a statistical test for the hypothesis that the survivor functions are equal

Appendix Figure 14: Kaplan-Meier survival function plots of time to an opioid use disorder diagnosis, by conditional combined high risk opioid use measure criteria



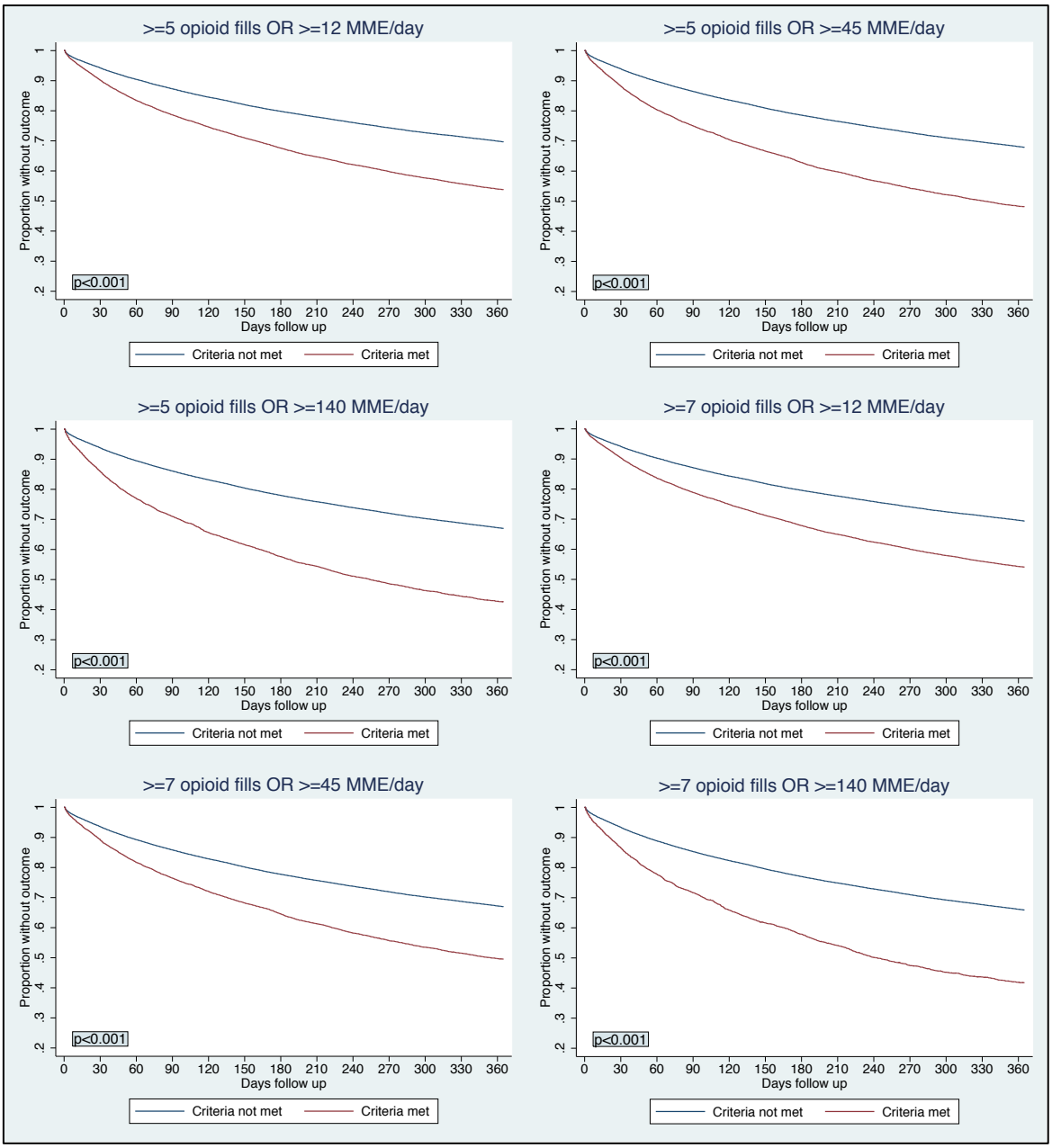
Note: p-values refer to a statistical test for the hypothesis that the survivor functions are equal

Appendix Figure 15: Kaplan-Meier survival function plots of time to any substance use disorder diagnosis, by individual high risk opioid use measure criteria



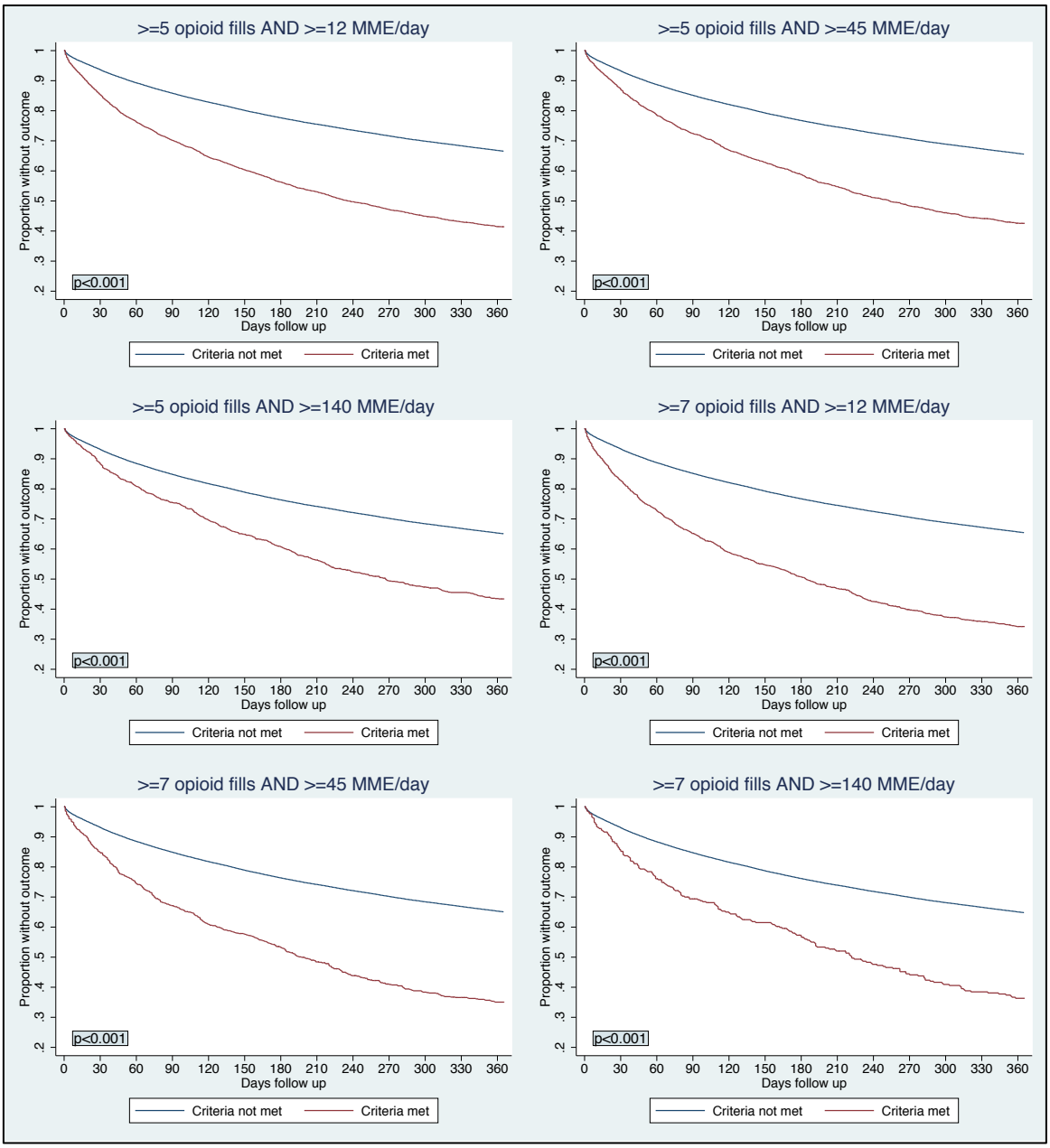
Note: p-values refer to a statistical test for the hypothesis that the survivor functions are equal

Appendix Figure 16: Kaplan-Meier survival function plots of time to any substance use disorder diagnosis, by unconditional combined high risk opioid use measure criteria



Note: p-values refer to a statistical test for the hypothesis that the survivor functions are equal

Appendix Figure 17: Kaplan-Meier survival function plots of time to any substance use disorder diagnosis, by conditional combined high risk opioid use measure criteria



Note: p-values refer to a statistical test for the hypothesis that the survivor functions are equal

Appendix Table 38: Kaplan-Meier estimates of unintentional acetaminophen overdose event, by opioid use criterion, represented as absolute risk differences and numbers needed to enroll

	Criterion met (N=69,667)	Follow-up time							
		30 days		90 days		180 days		365 days	
	n (%)	ARD	NNE	ARD	NNE	ARD	NNE	ARD	NNE
Individual measures									
≥5 opioid fills	5525 (7.9%)	0.0003	3924	0.0004	2549	0.0002	5977	0.0023	442
≥12 MME/day	19926 (28.6%)	0.0000	40721	0.0002	5834	0.0003	3974	0.0011	909
≥45 MME/day	7541 (10.8%)	0.0002	6637	0.0005	2096	0.0002	5803	0.0012	820
≥140 MME/day	1980 (2.8%)	-0.0001	-	0.0007	1460	0.0003	3957	0.0036	275
NC MLIP standard: ≥7 opioid fills	1703 (2.4%)	0.0005	2150	0.0015	660	0.0011	921	0.0019	526
Combined measures (unconditional)									
≥5 opioid fills or ≥12 MME/day	20404 (29.3%)	0.0001	10782	0.0002	4371	0.0003	3386	0.0013	767
≥5 opioid fills or ≥45 MME/day	10545 (15.1%)	0.0003	3369	0.0006	1721	0.0003	2915	0.0017	593
≥5 opioid fills or ≥140 MME/day	6336 (9.1%)	0.0002	4862	0.0005	2075	0.0002	4516	0.0028	356
≥7 opioid fills or ≥12 MME/day	19970 (28.7%)	0.0000	41528	0.0002	5883	0.0002	4018	0.0011	914
≥7 opioid fills or ≥45 MME/day	8370 (12.0%)	0.0003	3865	0.0007	1476	0.0004	2830	0.0014	700
≥7 opioid fills or ≥140 MME/day	3336 (4.8%)	0.0002	5754	0.0009	1095	0.0005	2121	0.0028	364
Combined measures (conditional)									
≥5 opioid fills and ≥12 MME/day	5047 (7.2%)	0.0001	14551	0.0002	4095	0.0000	24600	0.0018	564
≥5 opioid fills and ≥45 MME/day	2521 (3.6%)	-0.0001	-	0.0000	74565	-0.0004	-	0.0018	565
≥5 opioid fills and ≥140 MME/day	1169 (1.7%)	-0.0001	-	0.0005	1977	0.0001	12605	0.0023	436
≥7 opioid fills and ≥12 MME/day	1659 (2.4%)	0.0005	2080	0.0016	640	0.0011	882	0.0020	503
≥7 opioid fills and ≥45 MME/day	874 (1.3%)	-0.0001	-	0.0008	1222	0.0004	2536	0.0010	1028
≥7 opioid fills and ≥140 MME/day	347 (0.5%)	-0.0001	-	0.0026	380	0.0022	453	0.0048	210

Note: ARD=Absolute risk difference; NNE=Number needed to enroll; MME=Milligram morphine equivalent; NC MLIP=North Carolina Medicaid lock-in program. ARD was calculated from Kaplan-Meier survival function models by subtracting the probability of experiencing the outcome event at a given time point among those below an opioid use measure threshold from the probability of experiencing the outcome event at that same time among those meeting the threshold. The NNE was calculated as (1 / ARD) and is interpreted as the number of individuals needed to enroll into a hypothetical MLIP program based on a given opioid use criterion in order to have the opportunity to prevent one outcome event.

Appendix Table 39: Kaplan-Meier estimates of any unintentional overdose event, by opioid use criterion, represented as absolute risk differences and numbers needed to enroll

	Criterion met (N=69,667)	Follow-up time							
		30 days		90 days		180 days		365 days	
	n (%)	ARD	NNE	ARD	NNE	ARD	NNE	ARD	NNE
Individual measures									
≥5 opioid fills	5525 (7.9%)	0.0039	254	0.0093	108	0.0158	63	0.0295	34
≥12 MME/day	19926 (28.6%)	0.0014	724	0.0044	226	0.0088	114	0.0178	56
≥45 MME/day	7541 (10.8%)	0.0021	468	0.0057	177	0.0098	102	0.0208	48
≥140 MME/day	1980 (2.8%)	0.0014	730	0.0070	144	0.0155	65	0.0322	31
NC MLIP standard: ≥7 opioid fills	1703 (2.4%)	0.0068	147	0.0103	97	0.0175	57	0.0379	26
Combined measures (unconditional)									
≥5 opioid fills or ≥12 MME/day	20404 (29.3%)	0.0016	628	0.0049	205	0.0092	109	0.0184	54
≥5 opioid fills or ≥45 MME/day	10545 (15.1%)	0.0026	380	0.0072	139	0.0121	83	0.0232	43
≥5 opioid fills or ≥140 MME/day	6336 (9.1%)	0.0034	293	0.0091	110	0.0164	61	0.0314	32
≥7 opioid fills or ≥12 MME/day	19970 (28.7%)	0.0014	728	0.0044	227	0.0088	114	0.0177	56
≥7 opioid fills or ≥45 MME/day	8370 (12.0%)	0.0024	408	0.0059	170	0.0104	96	0.0212	47
≥7 opioid fills or ≥140 MME/day	3336 (4.8%)	0.0039	254	0.0086	117	0.0171	58	0.0359	28
Combined measures (conditional)									
≥5 opioid fills and ≥12 MME/day	5047 (7.2%)	0.0036	280	0.0085	117	0.0156	64	0.0294	34
≥5 opioid fills and ≥45 MME/day	2521 (3.6%)	0.0045	224	0.0085	117	0.0153	65	0.0333	30
≥5 opioid fills and ≥140 MME/day	1169 (1.7%)	0.0026	381	0.0072	138	0.0140	71	0.0281	36
≥7 opioid fills and ≥12 MME/day	1659 (2.4%)	0.0070	142	0.0107	93	0.0182	55	0.0394	25
≥7 opioid fills and ≥45 MME/day	874 (1.3%)	0.0088	114	0.0137	73	0.0210	48	0.0522	19
≥7 opioid fills and ≥140 MME/day	347 (0.5%)	0.0041	245	0.0096	105	0.0134	75	0.0310	32

Note: ARD=Absolute risk difference; NNE=Number needed to enroll; MME=Milligram morphine equivalent; NC MLIP=North Carolina Medicaid lock-in program. ARD was calculated from Kaplan-Meier survival function models by subtracting the probability of experiencing the outcome event at a given time point among those below an opioid use measure threshold from the probability of experiencing the outcome event at that same time among those meeting the threshold. The NNE was calculated as (1 / ARD) and is interpreted as the number of individuals needed to enroll into a hypothetical MLIP program based on a given opioid use criterion in order to have the opportunity to prevent one outcome event.

Appendix Table 40: Kaplan-Meier estimates of opioid use disorder diagnosis, by opioid use criterion, represented as absolute risk differences and numbers needed to enroll

	Criterion met (N=69,667)	Follow-up time							
		30 days		90 days		180 days		365 days	
	n (%)	ARD	NNE	ARD	NNE	ARD	NNE	ARD	NNE
Individual measures									
≥5 opioid fills	5525 (7.9%)	0.0138	73	0.0296	34	0.0523	19	0.0900	11
≥12 MME/day	19926 (28.6%)	0.0028	356	0.0107	93	0.0211	47	0.0404	25
≥45 MME/day	7541 (10.8%)	0.0049	203	0.0163	61	0.0310	32	0.0591	17
≥140 MME/day	1980 (2.8%)	0.0127	79	0.0318	31	0.0532	19	0.1002	10
NC MLIP standard: ≥7 opioid fills	1703 (2.4%)	0.0146	68	0.0374	27	0.0684	15	0.1161	9
Combined measures (unconditional)									
≥5 opioid fills or ≥12 MME/day	20404 (29.3%)	0.0034	298	0.0117	86	0.0222	45	0.0424	24
≥5 opioid fills or ≥45 MME/day	10545 (15.1%)	0.0082	122	0.0208	48	0.0371	27	0.0664	15
≥5 opioid fills or ≥140 MME/day	6336 (9.1%)	0.0132	76	0.0296	34	0.0514	19	0.0893	11
≥7 opioid fills or ≥12 MME/day	19970 (28.7%)	0.0028	352	0.0108	93	0.0211	47	0.0405	25
≥7 opioid fills or ≥45 MME/day	8370 (12.0%)	0.0060	167	0.0184	54	0.0349	29	0.0643	16
≥7 opioid fills or ≥140 MME/day	3336 (4.8%)	0.0133	75	0.0325	31	0.0589	17	0.1041	10
Combined measures (conditional)									
≥5 opioid fills and ≥12 MME/day	5047 (7.2%)	0.0132	76	0.0289	35	0.0522	19	0.0897	11
≥5 opioid fills and ≥45 MME/day	2521 (3.6%)	0.0124	81	0.0306	33	0.0576	17	0.1048	10
≥5 opioid fills and ≥140 MME/day	1169 (1.7%)	0.0160	62	0.0361	28	0.0626	16	0.1185	8
≥7 opioid fills and ≥12 MME/day	1659 (2.4%)	0.0147	68	0.0375	27	0.0694	14	0.1177	8
≥7 opioid fills and ≥45 MME/day	874 (1.3%)	0.0155	65	0.0418	24	0.0734	14	0.1308	8
≥7 opioid fills and ≥140 MME/day	347 (0.5%)	0.0190	53	0.0575	17	0.0811	12	0.1555	6

Note: ARD=Absolute risk difference; NNE=Number needed to enroll; MME=Milligram morphine equivalent; NC MLIP=North Carolina Medicaid lock-in program. ARD was calculated from Kaplan-Meier survival function models by subtracting the probability of experiencing the outcome event at a given time point among those below an opioid use measure threshold from the probability of experiencing the outcome event at that same time among those meeting the threshold. The NNE was calculated as (1 / ARD) and is interpreted as the number of individuals needed to enroll into a hypothetical MLIP program based on a given opioid use criterion in order to have the opportunity to prevent one outcome event.

Appendix Table 41: Kaplan-Meier estimates of any substance use disorder diagnosis, by opioid use criterion, represented as absolute risk differences and numbers needed to enroll

	Criterion met (N=69,667)	Follow-up time							
		30 days		90 days		180 days		365 days	
	n (%)	ARD	NNE	ARD	NNE	ARD	NNE	ARD	NNE
Individual measures									
≥5 opioid fills	5525 (7.9%)	0.0872	11	0.1625	6	0.2187	5	0.2567	4
≥12 MME/day	19926 (28.6%)	0.0380	26	0.0813	12	0.1163	9	0.1518	7
≥45 MME/day	7541 (10.8%)	0.0339	30	0.0759	13	0.1102	9	0.1530	7
≥140 MME/day	1980 (2.8%)	0.0362	28	0.0792	13	0.1262	8	0.1821	5
NC MLIP standard: ≥7 opioid fills	1703 (2.4%)	0.1066	9	0.2014	5	0.2627	4	0.3144	3
Combined measures (unconditional)									
≥5 opioid fills or ≥12 MME/day	20404 (29.3%)	0.0410	24	0.0867	12	0.1224	8	0.1586	6
≥5 opioid fills or ≥45 MME/day	10545 (15.1%)	0.0580	17	0.1146	9	0.1573	6	0.1972	5
≥5 opioid fills or ≥140 MME/day	6336 (9.1%)	0.0793	13	0.1511	7	0.2035	5	0.2437	4
≥7 opioid fills or ≥12 MME/day	19970 (28.7%)	0.0383	26	0.0821	12	0.1172	9	0.1528	7
≥7 opioid fills or ≥45 MME/day	8370 (12.0%)	0.0451	22	0.0938	11	0.1321	8	0.1744	6
≥7 opioid fills or ≥140 MME/day	3336 (4.8%)	0.0692	14	0.1362	7	0.1916	5	0.2416	4
Combined measures (conditional)									
≥5 opioid fills and ≥12 MME/day	5047 (7.2%)	0.0837	12	0.1565	6	0.2137	5	0.2511	4
≥5 opioid fills and ≥45 MME/day	2521 (3.6%)	0.0624	16	0.1271	8	0.1798	6	0.2300	4
≥5 opioid fills and ≥140 MME/day	1169 (1.7%)	0.0488	20	0.0936	11	0.1563	6	0.2165	5
≥7 opioid fills and ≥12 MME/day	1659 (2.4%)	0.1056	9	0.1991	5	0.2604	4	0.3120	3
≥7 opioid fills and ≥45 MME/day	874 (1.3%)	0.0841	12	0.1769	6	0.2319	4	0.3001	3
≥7 opioid fills and ≥140 MME/day	347 (0.5%)	0.0780	13	0.1530	7	0.1947	5	0.2847	4

Note: ARD=Absolute risk difference; NNE=Number needed to enroll; MME=Milligram morphine equivalent; NC MLIP=North Carolina Medicaid lock-in program. ARD was calculated from Kaplan-Meier survival function models by subtracting the probability of experiencing the outcome event at a given time point among those below an opioid use measure threshold from the probability of experiencing the outcome event at that same time among those meeting the threshold. The NNE was calculated as (1 / ARD) and is interpreted as the number of individuals needed to enroll into a hypothetical MLIP program based on a given opioid use criterion in order to have the opportunity to prevent one outcome event.

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