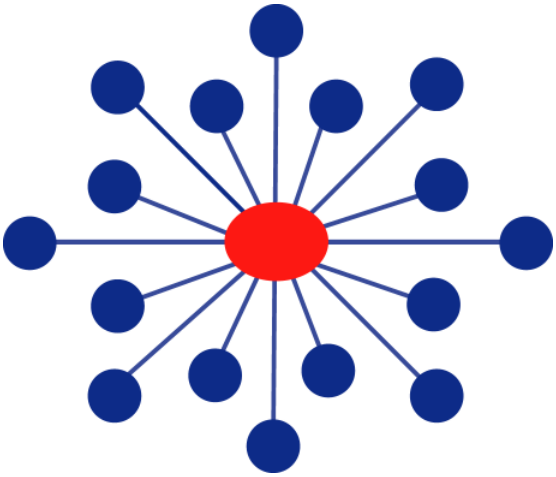

NIDA CTN Protocol 0084-OT

Developing a Prescription Opioid Registry across Diverse Health Systems

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1.0 List of Abbreviations

CDC – Centers for Disease Control

CMS – Centers for Medicaid and Medicare Services

ED – Emergency Department

EHR – Electronic Health Record

HCSRN – Health Care System Research Network

HSN – Health Systems Node

HEDIS - Healthcare Effectiveness Data and Information Set

ICD-9 and ICD-0 -International Statistical Classification of Diseases

KP – Kaiser Permanente

MOUD – Medication for opioid use disorder

OHSU – Oregon Health Sciences University

OUD – Opioid use disorder

PBRN - Practice Based Research Network (PBRN)

SUD - Substance use disorder

VDW – Virtual Data Warehouse

2.0 Study Synopsis

2.1 Background

Prescription opioid use has played a pivotal role in the opioid crisis, and as the prescribing environment becomes more conservative, there are important questions about how patterns of opioid use have changed and how this may impact patients with substance use disorder (SUD). To our knowledge, no study has established an EHR-based prescription opioid registry across ten diverse health systems with common data algorithms and with the flexibility to address multiple questions of opioid use and opioid use disorder (OUD). Nationally, the number of opioid prescriptions has fallen between 2013 and 2016, [1] and federal opioid prescribing guidelines has resulted in an even more quickly changing prescribing environment. At the same time, guidelines have not specifically addressed tapering strategies for reducing opioid doses, and we know little about how patients are being tapered, particularly patients with SUD.[2] There is also interest in understanding how prescribing for acute pain and after surgical procedures is related

to risk factors for (OUD), such as developing long term use of opioids. Finally, optimal time of buprenorphine treatment is unknown, yet there are methodological challenges for observational studies on this topic. Studies that can leverage large population level data are needed to address these priorities, and registries and robust electronic health record (EHR) data are increasingly cited as valuable resources to address critical research questions with high efficiency.[3]

2.2 Study Objectives

The goal of the proposed research is to develop a prescription opioid registry across ten diverse health systems with harmonized electronic health record (EHR) data, and leverage it to answer several key 'next step' research questions in response to the opioid crisis. The registry will include medications prescribed for treatment of OUD, including buprenorphine products.

2.3. Study Design and Outcomes

Aim1. The proposed study establishes a prescription opioid registry using EHR dispensation data from 2012-2017 across 10 health systems to identify algorithms and data elements that will be harmonized in a distributed data architecture. The registry will be used in the following aims.

Aim 2a. This aim examines opioid use patterns over 2012-2017 to examine changes during the evolving prescribing environment. We will examine differences in rates by age, gender, and race/ethnicity.
Aim 2b. We will examine categories of tapering (e.g. decreased opioid use) among prescription opioid patients, and whether faster taper rates are associated with adverse events (e.g. overdose, mortality).
Aim 2c. We will examine if patients with SUD or psychiatric conditions are less like to taper opioid use, compared to patients without those conditions.

Aim 3. We will examine how dispensations post-surgery and for acute pain are related to subsequent long term opioid use and opioid dosage levels, which are risk factors for OUD and overdose.

Phase 2, Aim 4. After recent discussions with the CTN, this aim is proposed as a Phase 2 analysis to identify different measures of buprenorphine retention, and explore the methods needed to examine the association to mortality rates.

2.4 Study Setting

This study includes 10 of the health systems in the Clinical Trials Network (CTN) Health Systems Node (HSN): Kaiser Permanente (KP) Northern California, KP Southern California, KP Colorado, KP Northwest, KP Mid -Atlantic States, Henry Ford Health System, Essentia Health, Geisinger, Meyers Health System, and Baylor Scott & White. There are four additional co-investigators: Jennifer McNeely, Greater New York Node; Dennis McCarty, Western States Node; and Steffani Bailey, OHSU and OCHIN Practice Based Research Network (PBRN), and Rowena Dolor, MD, Mid Southern Node (pending agreement). These co-investigators are

experts in treatment for OUD, as well as EHR based research, and will advise on how the study protocol can be extended to nodes outside of the HSN, including PBRNs.

The proposed registry will allow the CTN to develop critical EHR based capability to assess and track various impacts of the opioid crisis. We propose to develop the registry initially within the HSN to maximize efficiency in the short study timeframe, but with potential to be expanded to other nodes in the future. The health systems represented in the opioid registry also provide treatment for OUD, predominantly sublingual buprenorphine.

2.5 Sample Size and Study Population

The overall patient population across all health systems is approximately 10 million. We will develop a registry of patients based on any opioid dispensation for years 2012-2017. With approximately 18% of adults filling an opioid prescription annually,[4] we will have an estimated 2,048,400 adults in the registry population. The participating health systems represent diverse geographic, patient demographic, and organizational characteristics.

2.6 Analyses

Aim 1 will focus on identifying the registry's data elements, constructing approximately 13 distributed data tables across health systems, and harmonizing the data elements, including quality checks across sites to identify inconsistencies. Available data domains include pharmacy dispensations (e.g. opioid, benzodiazepine), demographics, inpatient and outpatient services utilization, clinical ICD9 and ICD10 diagnoses, and mortality. The registry will have a flexible structure that will allow us to address multiple research questions on opioid use and OUD, and can be retained for future studies of SUD as well.

Aim 2a will use interrupted time series to examine trends across time. Aim 2b will use repeated measures analysis to examine how tapering may be associated with adverse events, and Aim 2c will use logistic regression to examine whether patients with SUD are less likely to decrease opioid use. Aim 3 will use logistic regression to examine whether different days' supply for acute and post-surgery is associated with long term opioid use, and different dosage levels (e.g. >90 morphine milligram equivalents per day).

In response to recent discussions with the CTN, Aim 4 is proposed as a Phase 2 aim. Preliminary work will be conducted at one site, KP Colorado, and then implemented in other sites. It seeks to address the priority of the optimal duration of buprenorphine treatment to reduce the risk of relapse, overdose, and mortality outcomes using observational data. Answering this question with a randomized trial raises ethical concerns, observational studies with large datasets can address these important questions relatively quickly. At the same time, observational studies pose their own methodologic challenges related to confounding, misclassification of exposure and outcome, and informative loss-to-follow-up. We will identify and quantify the potential for these sources of bias and then conduct analyses to address primary question of interest. KP Colorado, an integrated health system has claims data, EHR data, buprenorphine dispensations, and information about methadone referrals and treatment. It is critical to understand these challenges and assess data quality in a rich data environment and

potential sources of bias to inform future trials, such as the CTN duration trial, and comparative effectiveness studies to definitively answer the question of interest.

3.0 Research Objective

The primary objective of this project is to develop a prescription opioid registry across ten diverse health systems that can be leveraged to inform the impact of the ongoing opioid crisis, improve clinical care for patients with OUD, and be a resource for future research questions on addiction. Specific study questions will also be addressed.

3.1 Specific Aims

Aim 1. Establish a prescription opioid registry across 10 health systems in California, Colorado, Minnesota, Mid-Atlantic states, Texas, Michigan, Pennsylvania, and Massachusetts for years 2012-2017. Develop the data architecture and test harmonized data elements for prescription opioids, benzodiazepines, buprenorphine, naltrexone, demographics, membership, comorbidity diagnoses, health services utilization, overdose, and mortality.

Aim 2. Characterize change in prescription opioid use from 2012-2017 across health systems. In consultation with expert clinical advisors, develop programmatic algorithms to identify specific rates of opioid tapering (e.g. 10% over 6 months, 10-20% over 6 months, >20% over 6 months). We hypothesize:

a. Opioid use will have decreased over time, with a steeper decrease after 2016 (when CDC guidelines were issued). We will examine whether there are differences in decreased use by gender, age, and race/ethnicity.
b. Examine how different taper rates are related to potential adverse outcomes (e.g. patients with faster taper rates will have greater risk of potential adverse outcomes relative to patients with slower tapers). Outcomes include opioid-related overdose, mortality, emergency department (ED) utilization, continued benzodiazepine use.
c. Patients with SUD and/or co-occurring psychiatric disorders (e.g. major depression, PTSD) will be less likely to taper opioid use.

Aim 3. Examine how the length of opioid prescribing (e.g. 3 or 7 days' supply) for acute pain in primary care and after common surgical events has changed over time, and examine association with subsequent long term use of prescription opioids, and by average daily dose.

In response to recent feedback from the CTN since our original concept was submitted, we are proposing an additional aim as a Phase 2 part of the study. This aim will be led by Jason Glanz, PhD, and Ingrid Binswanger, MD, at Kaiser Permanente Colorado and extends the study by one year.

Phase 2-Aim 4. Assess how different lengths of buprenorphine retention are related to mortality. Among patients who have initiated buprenorphine treatment for OUD from 2012 to 2016, we will:

a. Assess the distribution of buprenorphine treatment retention and number of treatment episodes by health system and patient characteristics.
b. Assess the rates of non-fatal overdose, fatal overdose, and all-cause mortality data across health systems, examining types of data available and source of data (e.g., cause-

of-death vs. fact-of-death, deaths during hospitalization vs. state death records).

c. Quantify the risk of mortality associated with different buprenorphine retention lengths accounting for the potential confounding by the baseline patients and health system characteristics identified in 4a.
d. Assess methodological challenges, including potential for loss to follow-up by examining the association between duration of treatment, length of health plan enrollment, and disenrollment from the health plan.
e. In a sub-cohort of patients from Kaiser Permanente Colorado, identify potential sources of treatment exposure misclassification after a buprenorphine discontinuation using clinical data and medical record review. We will identify naltrexone treatment and treatment through contracted methadone treatment clinics.

4.0 Significance

Opioid Crisis. The United States continues to face an opioid crisis, with increasing rates of opioid misuse and overdose.[5] While opioid prescribing has decreased nationally since 2012,[6,7] nearly half of all U.S. opioid overdose deaths involved a prescription opioid in 2016.[5] Approximately 2 million people had a prescription OUD in 2015,[8] and more than 15,000 people had a fatal overdose related to prescription opioids,[9] higher than in 2014.[10] In addition, misuse of prescription opioids is a risk factor for heroin use.[11]

Changes in Prescription Opioid Environment. In 2016 the Centers for Disease Control (CDC) and Prevention issued guidelines for opioid prescribing that included opioid dosing and risk mitigation strategies, and health systems have also implemented similar initiatives. Prescribing policies have become more restrictive and national data indicate the number of opioid prescriptions have decreased since 2013,[1] as well as dosage.[6,12] However, although the continued increase in opioid misuse and overdose is largely due to illicit and synthetic opioids (e.g. heroin and fentanyl), prescription opioids remain a main driver of misuse.[13,14] Many patients who have gone on to develop OUD initiated use with prescription opioids for pain, and progressed to heroin use.[11]

Opioid Tapering. Guidelines have not specifically addressed tapering strategies for reducing doses, and we know little about how patients are being tapered and the impact of tapering on the patient.[2] Most research to date has been with smaller samples or studies of pain programs.[15,16] A recent review found that dose reduction may be related to improvements in function and quality of life for some patients, but the evidence was considered low quality.[15] Previous and current studies of tapering have typically examined clinic interventions, or a single health system. Large scale observational studies have been recommended to examine population level impacts, particularly for rare adverse events such as overdose.[15] Currently, there are no standard protocols for decreasing use and individual physician's taper strategies can vary widely. Slow tapers may leave patients at high doses longer than necessary, whereas rapid tapers may result in unintended consequences, and there have been no published studies of slow vs. rapid tapers.[17] Concern about the potential for forced tapers have led to statements by experts on the risks.[18] Thus, we are lacking critical information on what is happening to patients as their opioid use changes. In addition, while studies have shown race/ethnic and gender disparities in opioid prescribing, typically with women having higher prescription opioid use[19] and less prescribing to African American and Hispanic patients, we know little about disparities in tapering, particularly for patients with psychiatric comorbidities or SUD, who are at

high risk of adverse events.[20]

Limits on Opioid Prescribing Amounts. Prescribing has changed not only for patients with long-term use, but also for patients with acute pain and undergoing certain surgical procedures, with suggested limitations on the number of days patients are prescribed opioids.[2] Few studies have examined changes in opioid prescribing after acute pain and for surgical events on a large scale across multiple health systems to address concerns about new iatrogenic OUD. The proposed study can leverage registry structure and methodology to address whether these changes associated with reduced of long term use and dosage levels, risk factors for OUD. Findings will inform whether there are unintended consequences for patients with opioid prescribing limits**.**

Buprenorphine Retention. The optimal duration of buprenorphine treatment to reduce the risk of relapse, overdose, and mortality outcomes is unknown, although generally a longer length of treatment is related to better opioid use outcomes,[21,22] as demonstrated by the Prescription Opioid Addiction Treatment Study, CTN0030.[23] The existing research on mortality suggests that buprenorphine is related to improved mortality.[21,22] A systematic review and meta-analysis of observational studies found more than three-fold higher off-treatment overdose mortality rates than on-treatment.[22] A recent Swedish study co-authored by Dr. Binswanger found reduced accidental overdose with use of buprenorphine.[24] However, retention in treatment remains a well-documented challenge. A recent study of Medicaid claims found that one quarter discontinue treatment within 90 days, and over 60 % within 180 days, and analyses of commercial claims have found similarly high rates of discontinuation.[25] The National Quality Forum's quality measure for OUD treatment emphasizes at least 180 days of treatment.[25,26] A recent commentary provided perspective from NIDA and CTN researchers on the importance of identifying who can discontinue MOUD and when as an important clinical and research priorities.[27]

Answering this question with a randomized trial raises ethical concerns, while observational studies with large datasets can address these important questions relatively quickly. At the same time, they pose their own methodologic challenges. Other factors can be related to discontinuation such as relapse, other substance use, inability to adhere to program stipulations, loss of insurance, cost, patient preference, provider practice, or health system policies. Given that patients do discontinue treatment in practice, and that evidence suggests it is unethical to randomize, we will examine discontinuation patterns to try identify who has positive outcomes after discontinuation. Thus, as a second phase, we examine the distribution of buprenorphine retention, associated patient and health system characteristics, and rates of mortality in an insured and diverse population. We will also examine reasons for discontinuation through detailed medical record review, and referrals to methadone. It is critical to understand these challenges and assess data quality and potential sources of bias for future trials and comparative effectiveness studies in this area. Thus, a primary focus will be methodological as a first step to inform future work by addressing methodological challenges that face observational studies such as bias due to loss to follow up, and capturing methadone use from other systems of care.

Advantages of Participating Health Systems. The registry will be developed across 10 health systems from the Health Systems Node: KP Northern California, KP Southern California, KP Colorado KP Northwest, KP Mid-Atlantic States (Maryland, Virginia, Washington DC), Essentia Health in Minnesota, Meyers Health System in Massachusetts, Henry Ford Health System in Detroit, MI, Geisinger in Pennsylvania, and Baylor Scott & White in Temple, Texas (Appendix

A). The proposed sites provide diverse patient populations, geographic representation, and organizational models (integrated vs. non-integrated). Henry Ford Health System has a large African American patient population, the Kaiser Permanentes in California have large Hispanic patient populations, Baylor Scott and White and Essentia serve rural populations. Other nodes have indicated interest in the registry and we are happy to include them at a later date, depending on ability to apply for future funding. We have included co-investigators from other nodes for this reason. Jason Glanz and Ingrid Binswanger from KP Colorado will lead the Phase 2-Aim4 on buprenorphine, collaborating closely with the study PI Campbell.

4.1 Why is this study important to the CTN?

The proposed registry will allow the CTN to continue to develop critical EHR based capability to assess and track impacts of the opioid crisis. It can be a CTN resource to quickly answer questions of clinical and policy importance on prescription opioid use, OUD, and co-occurring substance use. We examine how tapering of opioid use may be related to opioid overdose, and mortality, as well as how prescribing limits are affecting risk factors for OUD. We also examine how retention on buprenorphine is related to mortality. The specific study questions proposed examine the impact of important policies on patient risk, and the implications for patient care including for those with OUD. Questions about how to study MOUD in diverse health systems using the EHR are critical, since observational studies can address important questions with relatively less cost and time than intensive trials.

In addition to answering the proposed questions, it lays the methodological groundwork for EHR based registries in other CTN nodes. The proposed study builds on CTN-0061, led by Dr. Campbell, which developed a prescription opioid registry at KP Northern California and identified important predictors of opioid misuse and overdose across the years 2011-2014 using EHR data.

To our knowledge, the project would be the only EHR based registry of prescription opioid use across diverse health systems with geographic representation across the U.S. Patients in the registry are those have, or who are at risk of developing, OUD, particularly those patients at high dosages. It includes EHR data combined with claims data, mortality, insurance data, and clinical information such as SUD and psychiatric. The registry offers considerable flexibility to study critical questions, and could be leveraged for future work. For example, with this multisite registry in place, it could be refreshed to examine when new measures are implemented in health systems (e.g. patient reported outcomes), new medications are available, or new policies instituted. The registry also has the capacity to be merged with other registries (e.g. Hepatitis C, HIV). The EHR algorithms would be available to be shared, and adapted by other health systems. The diversity of the health systems offers the unique ability to examine race/ethnic disparities in patient populations too small in single health systems, and offers geographic and organizational diversity.

This study reflects the expansion of the CTN to include EHR data studies and findings could stimulate concepts for trials (e.g. new medications or interventions) and comparative effectiveness studies. In order to advise on how the study could be expanded to non-HSN node sites in the future, we have four co-investigators from other Nodes, including PBRNs.
We propose to develop the registry initially within the HSN to maximize efficiency in the short study timeframe, but with potential to be expanded to other nodes in the future.

5.0 Methods

We proceed in two stages: 1) develop the data architecture and harmonize data elements, and 2) leverage the registry to answer important questions on the opioid crisis. The methods of the first stage will entail algorithm development and data quality checks across the health systems by members of the analytic team. The studies in the second stage of the project are observational, consisting of analyses with the registry data.

5.1 Study Team

The study team is led by Cynthia Campbell, PhD, a Research Scientist at KP Northern California and the PI of the earlier Opioid Registry, CTN-0061. Tom Ray, MBA, is the lead analyst and who will be working closely with Dr. Campbell and the other Site PIs on the registry architecture. Sujaya Parthasarathy, PhD, is a health economist at KP Northern California. Andrea Altschuler, PhD, will manage the project across the different health systems, as she did with CTN-0072. Each health system as a research division with embedded investigators collaborating on the project aims, and the site PIs all bring expertise in EHR data analyses, and substance use. Investigators at KP Colorado, Ingrid Binswanger, MD, and Jason Glanz, PhD, are collaborating with Dr. Campbell to lead Phase 2-Aim 4 to examine buprenorphine retention and mortality. Dr. Binswanger is an Addiction Medicine physician with several NIH and CDC funded projects examining opioid use, and Dr. Glanz is an epidemiologist with expertise in using EHR data to examine treatment for overdose and prescription OUD.

The KP systems, along with Henry Ford Health System and Essentia have collaborated on other multisite studies, most recently on CTN-0072. That project was completed on time and budget in the projected 15-month timeline and produced seven manuscripts that are forthcoming in Substance Abuse Journal. We are confident that working with colleagues from three additional health systems that also employ the HCSRN VDW distributed data model will result in an equally successful collaboration to understand the impact of dose reduction/opioid tapering on patients.

5.2 Study Timeframe

The original study timeframe is 24 months, however if the Phase 2-Aim 4 moves forward, the study would be extended by one year.

5.3 Data Source

The data source for the registry is the Health Care Systems Research Network (HCSRN) Virtual Data Warehouse (VDW), which combines and harmonizes EHR data, claims data, and mortality data across the health systems.[28] All health systems in the registry are members of the HCSRN, and participate in the VDW. The VDW currently encompasses twelve data domains, including pharmacy data, data, membership, provider assigned diagnoses, inpatient and outpatient health services utilization as well as claims data and mortality data (Appendix B). Programmers at each site transform EHR and claims data elements from local data systems to a VDW standardized set of variable definitions, names, and codes. The common structure allows for programming code developed at one site to be used at other sites to extract and analyze data

for a research. The VDW serves as the source of standardized data from a variety of data systems in each HCSRN site. The VDW's distributed data model offers an effective means of protecting the identity of patients, providers, and health plans while allowing researchers and analysts to access data from much larger populations than they would otherwise be able to access within their own institution. This federated model with harmonized data elements facilitates multisite research.

5.4 Registry architecture, data extraction

Registry Architecture. Aim 1 focuses on the data architecture of the registry, which we describe here (the remaining aims leverage this architecture to answer specific study questions). The registry will follow a distributed data approach similar to those used in the VDW, and other large data efforts (e.g. the FDA Sentinel, FDA Vaccine Safety Data Link). It will consist of several relational data tables reflecting different domains and related data elements. Each health system will house its own version of the registry. The structure of these relational tables will allow analyses to be flexible for future research questions, when more specific code will use the data elements contained in these codes to create measures relevant to specific questions. We anticipate approximately 13 data tables.

The registry will be developed by extracting data from the VDW, with initial identification based on pharmacy data (e.g. dispensations). Data elements to be included are based on prior work by the study team as well as external literature (Appendix C). These will be discussed and finalized among the study team, including the Site PIs from each health system and co-investigators from other nodes. Tom Ray, the lead analyst will work closely with the analysts at each site to locate all of the necessary data elements within their respective electronic health records (EHR) and develop the code that will be distributed and adapted at each site. This will be an iterative process, with ongoing data quality checks by study investigators.

Table 1. Registry Table Domains	
1	Opioid Use
2	Benzodiazepine Use
3	Demographics
4	Membership
5	Census
6	Mortality
7	Utilization
8	Diagnoses
9	Procedure
10	Provider
11	Person time denominator
12	Monthly opioid use

The registry will contain the years 2012-2017 to capture a time of considerable change in prescribing practices (currently we do not propose 2018 since there would be no observable follow up time). Thus, all adult patients with at least one opioid dispensation for years 2012,

2014, 2015, 2016, 2017 will constitute the registry base, and these data will be combined with the other medication data, inpatient and outpatient utilization, ICD9 and ICD10 diagnoses and mortality (see measures below). Patients who are identified as having cancer through the Tumor registry will be excluded. Some analyses will not include 2012, since the first year is often used as a 'clear period' to establish criteria such health system membership, or clinical diagnoses. The analyses for aim 4 will focus on 2012 to 2016 to allow sufficient time for updated mortality data to be acquired. Dispensations records can be aggregated to daily or monthly use measures as specific research questions dictate. This structure allows flexibility to answer multiple questions. As is done with distributed data structures, the registry and relevant analyses will be maintained locally, except for select analyses on rare outcomes (e.g. overdose) when data will be combined across sites. These decisions will evolve with discussion among the study team as the analyses are deployed. Using this opioid fill table and previously developed algorithms, we can identify patient-level daily opioid use when required for specific research questions.

Measures

Demographics: age, gender, race/ethnicity, neighborhood deprivation index at census track level (geographical measure of socioeconomic status based on patient's home address in combination with the 2006-2010 American Community Survey (ACS) collected by the U.S. Census Bureau[15,16]).[17]

Prescription opioid use: we will extract all opioid dispensations made at health system outpatient pharmacies during 2012-2017 (Table 1). We exclude opioid formulations used primarily as antitussives, anesthetics, antihistamines, antidiarrheals, and injectables (Appendix D). Days' supply will be included, and the average morphine milligram equivalent (MME) per day will be calculated using Centers for Disease Control conversion factors, as we have done in prior research.[4]

Medication for OUD. We will capture buprenorphine dispensations, naltrexone, and for KP Colorado only, we will also capture methadone referrals and claims.

Benzodiazepine use: We will identify monthly use of benzodiazepines based on days' supply and calculate mean lorazepam-equivalent monthly dose by converting the strength to lorazepam equivalents in mg.[29]

Pain diagnoses: For Aim 3, new visits for common pain conditions (e.g. joint pain, back pain, headache, neck pain, musculoskeletal, etc.) will be identified following the methodology of Mundkur, 2017.[30]

Opioid use disorder: ICD9 (304.x, 305.X) and 10 codes (F11)

Non-opioid substance use disorders: alcohol, tobacco, cannabis, cocaine, methamphetamine.

Comorbid diagnoses: As in prior research,[18] we will identify diagnoses for one or more of thirteen chronic conditions: arthritis, hypertension, chronic pain, asthma, ischemic heart disease, congestive heart failure, stroke/cerebrovascular accident, Parkinson's Disease, end-stage renal disease, osteoporosis, and chronic obstructive pulmonary disease. We will also identify the following *psychiatric conditions*[18]: attention deficit disorders, anxiety disorder, autism, bipolar disorder, dementia, depression, other psychoses, personality disorder, schizophrenia,

Health services utilization: outpatient: emergency department, primary care, substance use treatment services; inpatient[30]: eight surgical procedures (cholecystectomy, appendectomy, inguinal hernia repair, anterior cruciate ligament reconstruction, rotator cuff tear repair, discectomy, mastectomy, and hysterectomy) following the methodology of Scully et al, 2018.[31]

Overdose and mortality: ICD9/10 codes for opioid related overdose; all-cause mortality from

health system and state death files.

5.5 Registry Population

Aim 1. The combined adult membership across the health systems is 11,380,000. Based on CTN0061 findings, 18% of adult members fill an opioid prescription annually, which would provide a registry population of approximately 2,048,400 adult members (Aim 1). This estimate excludes patients with cancer, as identified through the Tumor table.

Aim 2a will use all patients in the registry over the study timeframe, and analyses will be conducted locally.

Aim 2b subsample will focus on patients who are tapering. Based on CTN0061 findings, we estimate we will have approximately 512,100 patients with long term use, and 35,847 with average daily dose >100mg across the sites; this will provide a robust sample size for proposed analyses. We have not yet tested the algorithms for the tapering categories, and there is no published literature on EHR identified tapering categories. We have based estimates on estimates in the literature on discontinuation rates, and on some preliminary work at KP Northern California that looked at a difference in dose across 6 months in preliminary data. Analyses will initially be done locally, but for rarer adverse events (e.g. ED visits) data will be combined across health system.

Aim 2c will examine sub-samples of patients with SUD or psychiatric disorders, and whether they are less likely to taper their opioid use. Based on CTN-0061, we estimate approximately 1300 patients will meet the minimum amount of MMEs long term (>50 mg), and who have a diagnosis of a SUD (e.g. cannabis, opioid, stimulant, alcohol). Analyses will be combined across health systems.

Aim 3 is a subsample of patients who have had a primary care visit or who have had select surgical procedures. We estimate the number will be similar based on studies by Mundkur and by Scully, respectively. Using .016% for the percent of patients with visits for acute pain in primary care, we would have approximately 160,000 patients. For the surgical analyses, we estimate .022% of patients, for approximately 220,000 patients. We will explore conducting analyses locally at each health system, as well as combined.

Phase2-Aim 4 will include patients who have initiated buprenorphine within the study years (approximately 1000 annually at Northern California). This Phase 2 aim will be presented in detail later, and reviewed in more depth in a future DSMB meeting, per Dr. Rosa.

6.0 Analysis Plan

Aim1 will focus on developing and harmonizing data elements across sites as described above in data architecture. This will consist of regular meetings with study investigators and analysts to develop the relevant measures and data algorithms, and conduct data quality checks (e.g. data completeness, outliers, etc.). Sites that use a mix of medication orders and dispensation data will have additional meetings and consultations with the study investigators and statisticians.

Aim 2a. Characterize change in prescription opioid use from 2012-2017 across health systems. We hypothesize opioid use will have decreased over time, with a steeper decrease after 2016 (when CDC guidelines were issued). We will examine whether there are differences in decreased use by gender, age, and race/ethnicity.

Aim 2a. Using the registry, we will determine the total morphine milligram equivalents (MMEs) dispensed to all patients in the registry for each month from 2013 – 2017. We will similarly calculate the total person months covered by the health plan for this time. To analyze the trend in overall opioid prescribing from 2013 to 2017, we will calculate the MMEs dispensed per person-month. Using this analytic dataset, we will plot MMEs per person-month over time, as well as for demographic and SUD diagnosis subgroups (e.g. by gender, age, and race/ethnicity, substance use dx) over time. These plots will indicate the trends in opioid prescriptions over time. We will use an interrupted time series design to determine if there is a distinct change in opioid prescribing pattern after 2015 (when we might expect a CDC policy impact). For these analyses, we will create a dichotomous ("pre/post") variable indicating if the calendar month is in years 2013-2015 or years 2016-2017. We will run an ordinary least squares regression with MME per person-month as the outcome variable, and include calendar month, the "pre/post" indicator variables and their interaction as predictors. A significant coefficient of the main effect of the "pre-post" indicator will imply a change in the mean level of MME and the coefficient of the interaction of the pre/post indicator variable with the calendar month will indicate whether there was a change in the rate (slope) of opioid prescription after 2015. To assess whether these trends differed by demographic subgroups (e.g. gender), we will include main effect (of gender) and two-way (change in levels) and three-way interactions (change in slope) of time, "pre/post" indicator, and the demographic characteristic (gender).

Aim 2b. Examine how different taper levels are related to potential adverse outcomes (e.g. patients with faster taper rates will have greater risk of potential adverse outcomes relative to patients with slower tapers. Outcomes include (e.g. opioid-related overdose, mortality use of the ED, continued benzodiazepine use), relative to those with slower tapers.

Aim 2b. We will first classify individuals into different taper categories based on every six-month period (starting with January, 2013) as follows: 1) calculate the total MMEs for the first 3-months and the second 3-month periods. 2) Calculate the percent difference between the two 3-month periods. 3) Categorize the percent difference into 3 tapering categories: 1) > 20% decrease 2) 10-20% decrease 3) < 10% decrease. We will repeat this process for each month of the study period (e.g. February 2013, March 2013…December 2017). We will examine the relationship between the tapering category thus defined and the outcome in the subsequent month (e.g. a patient's outcome for September 2017 will include as a predictor variable, the difference in MME percentage (defined as one of the 3 categories above) between March-May 2017 and June-Aug 2017). Monthly records in which the patient had no opioid use in the prior six months will be excluded from the analysis. Monthly records in which a patient was not a member of the health plan in the current month and each of the prior six months will also be excluded. Thus, the analytic dataset will include one record per person per month from 2013 to 2017 and every patient will have up to 60 repeated measures. (Note: Patients who increase use will be retained in the registry for future use, but will not be part of these analyses.) To determine the relationship between tapering (change in opioid dose) and adverse outcomes, we will use a repeated measures design with appropriate distribution (e.g. logistic regression for ED use),

using a Generalized Estimating Equations approach to account for correlation between multiple records per person. The predictors of interest will be a measure of the patient's recent overall use of opioids and a measure of their recent change in opioid use, regardless of whether they are using at a high dose or a low dose. For example, if the coefficient for the faster taper category listed above is greater than the slow taper category, this would indicate that faster tapering of opioid use is associated with increased odds of the adverse outcome. The definitions of the opioid use and tapering variables may be modified in response to preliminary analyses and input from the project team, including the number of months of prior usage that is considered as a potential predictor and the specific parameterization of the change-in-use (tapering) variable. For example, the change from one to two months may be a more sensitive measure of tapering given fluctuations in dose; we will explore sensitivity analyses of the tapering algorithm with shorter time frames (e.g. one month).

Aim 2c: We will examine if patients with substance use disorders or psychiatric conditions are less like to taper their opioid use, compared to patients without those conditions.

Aim 2c. We will identify individuals who used at least 50 MMEs of opioids for three consecutive months during the period January 2013 – December 2017. The first occasion that a person met this criterion will be considered the "index period". For analyzing the relationship between tapering and comorbidity, we will retain only those individuals with continuous health system membership from 12 months prior to 3 months post-index period. We will create a dichotomous indicator of SUD or psychiatric disorder during the index period (e.g. =1 if at least one SUD diagnosis, 0 otherwise). To address confounding, we will perform a 1:1 match between those with a diagnosis (Group 1 patients) and those without (Group 2) using a propensity score approach. Key variables used in calculating the propensity score will be the total MMEs in the index period, the slope of the monthly MMEs from month 1 to month 3 of the index period (which will be determined using an ordinary least squares regression), and the total MMEs in the year prior to the start of the index period, with the main goal being that the two cohorts have similar opioid use prior to, and during, the index period. If possible, we will insist that there is exact matching on the first calendar month of the index period. For each patient, we will compare the total MMEs in the 3-month post-index period to the total MMEs in the index period. We will create a dichotomous variable (=1 if opioid use decreased compared to the index period, 0 otherwise). Logistic regression will be used to determine if SUD or psychiatric comorbidity (analyzed in separate models) is a predictor of the opioid tapering.

Aim 3. Examine how the length of opioid prescribing (e.g. 3 or 7 days' supply) for acute pain in primary care and after common surgical events has changed over time, and examine association with subsequent long term use of prescription opioids, and by average daily dose

Aim 3. To examine changes prescribing patterns in initiation of opioid use, we will identify the first instance per person (from 2012-2017) of a receipt of one of the pain diagnoses of interest associated with a primary care visit. Persons with another such pain diagnosis in the prior 6 months, or any opioid fill, will be excluded. We will retain those persons who received an opioid medication within 1 week after their index pain diagnosis.[30] Persons without continuous health plan membership from 6 months before, to 3 months after, their index diagnosis will be excluded. We will analyze the distribution of days' supply of the index fill to determine the most appropriate model for assessing whether days' supply for index fills has changed over time. We will examine both the proportion of patients with 3-day and 7-day supply as well as the proportion of total prescriptions for 3-day and 7-day supply using the independent t-test. We

expect a lower rate of 7-day supply after 2016. To model the association of days-supply of first prescription with long-term use, we will use all outpatient opioid fills for these patients in the 90 days after their index pain diagnosis. We will create a dichotomous variable identifying long term use, defined as continued opioid use for 90 or more days following index pain diagnosis; this is the outcome variable. (This opioid use measure will not include their index fill.). The key predictor of interest will be days' supply of the index fill. We will create a dichotomous indicator (=1 if 3-day supply, 0 if 7-day supply). We will use logistic regression to examine the significance of this coefficient on the likelihood of long-term use. We will replicate these analyses for the subgroup of patients who underwent a surgical procedure with the index date and fill defined with reference to the procedure date. To understand the relationship of days' supply to dosage level of long-term use, we will also create a multi-level indicator indicating whether long-term use is at a high, medium or low dosage level in MME, and conduct a proportional odds regression with this measure as the ordinal dependent variable; days' supply will remain the predictor of interest.

Phase 2, Aim 4. Examining buprenorphine retention and mortality. Please note we the methods for this aim in brief, since it was recently added per the CTN's request. Per Dr. Rosa, a full analysis plan will be provided for a future DSMB review.

Analysis 1: Examine distribution of differing lengths of buprenorphine retention and associated patient and health system characteristics.
Analysis 2: Assess the rates of non-fatal overdose, fatal overdose, and all-cause mortality data across health systems, examining types of data available and source of data (e.g., cause-of-death vs. fact-of-death, deaths during hospitalization vs. state death records).
Analysis 3. Quantify the risk of mortality associated with different buprenorphine retention lengths accounting for the potential confounding by the baseline patients and health system characteristics identified in 4a.
Analysis 4: Assess methodological challenges, including potential for loss to follow-up by examining the association between duration of treatment, length of health plan enrollment, and disenrollment from the health plan
Analysis 5: Through medical record chart review and sensitivity analyses at KP Colorado, assess potential for misclassification, confounding, selection bias and informative loss to follow-up.

This aim uses a sub-sample of the registry, those who have initiated buprenorphine treatment between 2013-2016 (we truncate at 2016 to allow for the lag in mortality data) to examine the distribution of buprenorphine retention, and mortality rates. Data elements will include the aforementioned elements in the opioid registry: Demographics, opioid dispensations, clinical diagnoses, buprenorphine dispensations, overdose (nonfatal) and mortality outcomes.
We will use integrated health plan enrollment data to establish periods during which patients are continuously enrolled in their health plan and receiving care. Establishing periods of continuous enrollment will help ensure that we are accurately capturing all health care encounters, including treatments, medications, comorbidities, overdoses and fatalities.

During periods of continuous enrollment, patients will accrue person-time follow-up that will be separated into two groups: time on buprenorphine treatment and time post buprenorphine treatment. The main exposure variable will be length of time on buprenorphine treatment, and outcomes (mortality, overdose) will be identified in the post treatment period. This will allow us to evaluate the association between duration of buprenorphine treatment and

overdose/mortality risk. It is important to stress that both follow-up time on treatment and follow-up time post treatment are needed for this analysis.

The enrollment data and ability to follow patients longitudinally is a unique feature of many of the integrated health systems in the HSN. Non-integrated health insurers and claims-based systems, in contrast, tend to lack the ability to follow patients for prolonged periods of time and would have difficulty assessing length of time on treatment. For example, in a claims-based system, a patient may be receiving buprenorphine treatment while insured, but then change insurance and resume treatment under a new insurance policy. In the claims data, the length of time on treatment would be artificially truncated due to loss to follow-up, leading to an underestimate of treatment duration. Such misclassification of treatment duration (the exposure) could lead to significantly biased results.

Misclassification of the outcome is another methodological obstacle to answering this question. Certain patients receiving treatment may be at higher risk for experiencing a relapse, losing insurance and overdosing after they lost insurance. Their duration of treatment would be shortened due to loss of insurance, and the outcome (overdose) may not be captured because these high-risk patients cannot be followed after losing insurance. If shortened treatment is associated with an increased risk for overdose, this type of loss to follow-up and outcome misclassification would also bias results.

To address the potential for treatment and outcome misclassification, we will conduct a medical record review at KP Colorado to identify treatments and outcomes that were not captured in the EHR. It should be stressed that the ability to conduct a detailed medical record review is another unique resource of the integrated health systems in the Health Systems Node. Claims-based systems, in contrast, have limited access to medical records.

We will first use the opioid registry data to examine statistical associations between duration of treatment, length of enrollment, and disenrollment from the health plan. In the data, some of the patients will appear to have stopped treatment, while others will disenroll from the health plan while receiving treatment. We will then select a sample of patients from each of these two groups for a medical record review. Using a medical record abstraction form developed at the aim's lead site (KP Colorado), trained abstractors will examine the medical records to identify other treatments received (buprenorphine, methadone, naltrexone) and overdose outcomes that were not captured in the EHR data. This will provide an estimate of exposure and outcome misclassification that can then be used in sensitivity analyses to adjust for potential bias. These results will also inform whether claims-based data, such as those in the Sentinel system, can be used to assess association between buprenorphine treatment length and mortality risk. In other words, if the exposure and/or outcome misclassification rates are high (> 10%), it would suggest that claims-based systems should not be used to answer this question since their ability to conduct a detail medical record review to validate exposures and outcomes is significantly limited.

To conduct these analyses, we will use logistic regression, Cox proportional hazards regression and Monte Carlo simulations.

Power

We have calculated power based on estimates from Northern California and our prior work. We assume power will be even higher for analyses where data will be combined across sites.

We will assume a significance level of .05 for all power calculations. Power analysis for the interrupted time series design (Aim 2a) follows a simulation-based approach.[32]. We will have 60 months of data of which 36 months are prior to the new CDC guideline. Informed by prior research,[12] we assume that the average opioid dose prior to 2016 was 60 MMEs with average taper rate of 22% and a variance of 5.7 MME. To detect a decrease of 10% in the mean dose and 40% faster taper rate post-2016, we will have a power of .85. For a higher decrease of 15% in the mean dose, the power will be .98. Power calculation for the repeated measures analyses (Aim 2b) will use the method proposed by Diggle et al.[33] We specify the Type I error rate (a), the smallest meaningful difference to be detected (d) or, in standard deviation units (D), power (p), measurement variation (s2), the number of repeated observations per person (60 in this study) and the correlation among the repeated observations (r).For a binary outcome such as ER use, based on 60 months data, the power will be .95 to detect a 5% difference between those with and without high taper with a sample size of 1489 and a worst-case correlation of .90 between repeated measures. The sample size will be lower (1327) for a lower correlation of .80.

Aim2c will compare the likelihood of tapering between those with and without a comorbid psychiatric or substance use problem among those who had at least 3 consecutive months of opioid dose > 50MME. To test hypotheses pertaining to tapering rates between these two groups, using the method proposed by Demidenko et al,[34] assuming a 60% tapering rate among those without a substance use problem and 4% substance use comorbidity and hypothesizing that those with comorbidities will have lower likelihood of tapering, we will have a power of .95 to detect a minimum odds ratio of 1.5 with a sample size of 9,620. To compare the difference in the proportion of individuals receiving 7-days' supply before and after 2016 (Aim 3), assuming that 50% of the patients receive a 7-days' supply before 2016, we will have a power of .95 to detect a 5% change in the days' supply post-2016 with a sample size of 2590 in each period. Power calculation for testing hypotheses pertaining to the relationship between likelihood of long-term use and days' supply of index fill will follow the work of Demidenko as before. Assuming that 30% of individuals have long-term use and 50% of patients receive 7-days' supply and hypothesizing that those with longer days' supply will have higher likelihood of long-term use, we will have a power of .95 to detect a minimum odds ratio of 1.5 with a sample size of 1549.

Power for Phase 2-Aim 4 will be determined pending CTN approval, and further DSMB review.

7.0 Reporting

Reports and publications that are published from this study will present results with blinded study sites, though they will be known to the study team.

8.0 Timeline

Please note there is only a Year 3 if Phase 1-Aim4 moves forwards

	Year 1				Year 2				Y3 for Aim 4			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Prepare and submit IRB application – all cites to cede to KP Northern California	x	x										
Data Use Agreement (DUA) preparation and submission for limited datasets	x	x	x									
IRB Approval		x										
DUA submissions from all sites			x									
Identify data elements	x	x										
Develop algorithms for data extraction, write and test distributed code	x	x	x									
Data extraction from VDW			x	x	x							
Prepare limited data sets												
Develop algorithms for data extraction for multisite analysis as appropriate												
Aim 1-3 analyses			x	x	x							
Data abstraction development and conduct for Aim 4						x	x					
Data extraction on mortality for Aim 4							x	x	x			
Data analyses for Aim 4								x	x			
Manuscript development				x	x	x	x	x	x	x	x	x
Report and manuscript preparation and dissemination							x	x	x	x	x	x

9.0 Confidentiality

In accordance with long-standing policy, all data collected as part of this study will be held in strict confidence. Only study staff will have access to the data collected as part of the study, and all employees who come in contact with these records sign an agreement to maintain confidentiality. All names are removed from research records; no identifying information will be used in any report or publication that is produced from this study. Data will only be presented in the aggregate. Data are kept under password protection on the secure, KP research office network and other health system networks (for their data).

Identifying information (e.g. health plan member numbers, name, address) will only be necessary to extract computerized administrative data from health system databases and medical records within each health system. During the data extraction, identifying information will only be available to the study programmer and only in non-readable, electronic formats.

We will control risks of disclosure of confidential study data by the following procedures: a) storing identifying information in secure, password protected files segregated from the registry; b) employing HIPAA standards to ensure that Group A identifying information is not included in the study database (e.g. exact date of birth); c) restricting access to identifying data to lead investigators and project programmers and only in electronic formats (i.e. no printed lists or computer screens with identifying information will be employed by the study).

Per HIPAA regulations, we will seek a waiver of the need for authorization for use of diagnostic information obtained via chart review/electronic data.

For select analyses with smaller subsamples and rarer outcomes (Aim 2b, Aim 3) data from across the health systems will be combined. These limited datasets will be transferred via secure file transfer to KP Northern California, where they will be stored on a secure KP Division of Research (DOR) server. The lead analyst at KP Northern California will review, combine, and apply quality assurance checks upon receiving the limited datasets produced at the sites and create the combined analysis dataset for further statistical analyses. The final analysis dataset, a limited dataset, will then be stored on the KP DOR server with access only by the study staff. Not all analyses will be combined. For the research questions that include the full registry (Aim 2a, 2c) analyses will be conducted in a distributed manner, meaning locally at each health system with standardized code developed by Northern California; this is often done with VDW multisite studies given the large size of the datasets.

10.0 Participant Recruitment

This is a data only study, therefore patients are not recruited into the study. Because of the estimated number of patient records which will be included in the analyses (N=~11,380,000) it would not be feasible to conduct the study and obtain informed consent from each individual to examine their medical records.

11.0 Informed Consent

We are requesting a waiver of informed consent and a waiver of authorization from our IRB for this study. No direct intervention or contact with member patients will occur. We will use data already collected from outpatient diagnostic and registration databases and the electronic medical record from each participating site. Further detail about the databases is provided in the Methods Section of the Proposal. Thus, we are requesting a waiver of informed consent and a waiver of authorization for that component of the study.

There are few potential risks associated with database/EHR based research to patients since only computerized records will be analyzed. The only risk is possible embarrassment by release of individually identifiable data, and every possible safeguard will be in place to ensure that patient data is kept strictly confidential. Only study staff will have access to the data collected as part of the study, and all employees who come in contact with these records sign an agreement

to maintain confidentiality. All names are removed from research records; no identifying information will be used in any report or publication that is produced from this study. Data will only be presented in the aggregate. Employee study staff in each Kaiser region and each respective non-Kaiser health system will be the only persons who access the data as a part of their tasks in extracting the data. Only limited datasets will be used for the analysis and these will be kept under password protection on the DOR local area network behind a firewall.

12.0 Risks and Benefits

12.1 Risks

The risk to participating in this study is minimal. The only risk to patients is loss of privacy; however, since each site is only employing datasets on HIPAA Compliant password protected folders behind each health systems firewall, these risks are negligible. We are confident that the procedures we have outlined to protect subjects will function effectively and that the anticipated benefits of the study to society as well as to the population of the health plan will outweigh the small potential risk to the individuals whose records are utilized for the research.

Only study staff at each health system will have access to the data collected as part of the study, and all employees who come in contact with these records sign an agreement to maintain confidentiality. All names are removed from research records; no identifying information will be used in any report or publication that is produced from this study. Data will only be presented in the aggregate. Employee study staff in health system will be the only persons who access the data as a part of their tasks in extracting the data. Only limited datasets will be transferred to the DOR for the analysis and these will be kept under password protection on the KP local area networks behind a firewall. Secure file transfer will be used to transfer datasets to KP Northern California DOR.

All manuscripts for publication will be reviewed by Dr. Tracy Lieu, Director, Division of Research, other health system research directors if requested, and the CTN publications committee.

12.2 Benefits of the study to participants and to society

It is not possible to predict whether or not individual study participants will receive any personal benefit from participating in this study. It is hoped that the information gained from this study will help us answer crucial questions about how the opioid crisis is evolving, risks for patients who use opioids and those with OUD, other SUDs, and answers to important questions about patient care.

12.3 Risks vs. Benefits

Individuals who are on long term opioid therapy are at risk for OUD, and rates of tapering opioids may be associated with adverse events, such as overdose. Little is known about the impact on patients while the prescribing environment has changed considerably in the last several years. Additionally, buprenorphine retention remains a challenge in real-world practice, and little is known about what characteristics are associated with favorable or unfavorable outcomes after buprenorphine discontinuation. This multisite study from diverse health systems provides an

opportunity to examine how these changes have impacted important patient measures related to the opioid epidemic and OUD. We also have the opportunity to advance the methods to examine optimal treatment duration of buprenorphine, which could improve care for patients with OUD. The minimal risks to participant confidentiality are more than justified by the potential significance of the study findings and by the strict safeguards we are using to protect participant privacy.

13.0 Safety monitoring

There are no physical and no emotional risks to patient safety. The only risks for patients are to confidentiality, and we will control risks of disclosure of confidential study data by the following procedures which are employed at each participating health system site: a) storing identifying information in secure, password protected files segregated from the study database and only within each region for the dataset for that region; b) employing HIPAA standards to ensure that the analysis dataset is a limited dataset; c) restricting access to identifying data to project programmers.

14.0 Research Study Sites

- Kaiser Permanente Northern California (California)
- Kaiser Permanente Southern California (California)
- Kaiser Permanente Colorado
- Kaiser Permanente Mid-Atlantic States (DC, Maryland, Virginia)
- Kaiser Permanente Northwest (Oregon)
- Baylor Scott & White Health (Texas)
- Essentia Health (Minnesota, North Dakota, Wisconsin, and Idaho)
- Geisinger (Pennsylvania)
- Henry Ford Health System (Michigan)
- Meyers Health System (Massachusetts)

The role of each site PI will be to be part of the Investigator team and meet at least monthly via phone with Dr. Cynthia Campbell. The first six months each site PI will work closely with his/her analyst and the other sites to finalize the study algorithms. The subsequent 12 months will be used for the data analyses, and in Year 02, the final report and manuscripts will be drafted and finalized and include implementation next steps. Additionally, each site PI will participate in ad-hoc meetings and electronic dialogues focused on finalizing the analytical plan and providing feedback on the final report and analyses. As the leader, Dr. Campbell's role will be to lead this effort and ensure that all of the study objectives are met within the timeframe. Manuscripts will be developed and led by investigative team members. The Phase 3 – Aim 4 is structured slightly different with investigators at KP Colorado leading the analyses for that aim. Drs. Glanz and Binswanger are experts in EHR analyses and OUD treatment, and bring their expertise to this aim. KP Colorado also has the ability to conduct the chart reviews to examine methadone use outside of their system to assess potential bias in the EHR data which will inform the larger EHR analyses.

15.0 Data Sharing

Researchers participating in the HSN sites proposed for this project have extensive experience working together, successfully collaborating on multisite projects within the HCSRN network (thus, including the Health Systems Node). Using the principles and standards set forth by the HCSRN, data sharing has been successfully and compliantly practiced across these health systems. Data sharing across these sites has occurred for feasibility testing, pilot projects, randomized clinical trials, retrospective data only studies, prospective primary data collection studies, pragmatic trials, and quality assessment or improvement activities. As a result of these past practices the HCSRN has established guiding principles and templates which are adhered to and used by HCSRN members, who use the HCSRN VDW data for collaborative research. The existing approved data sharing resources will be used as templates for the proposed project.

Summarized below are the HCSRN data sharing guiding principles that incorporate the required federal elements for any data sharing plan and which we will adhere to for the successful execution of this project.

HCSRN members agree upon the following guiding principles:

- ✓ Each HCSRN member organization is responsible for ensuring its own staff are:
  - o Adequately familiar with federal guidance regarding methods for de-identification of protected health information (PHI) in accordance with the HIPAA privacy rule.
- ✓ Adhering to their local center's process for determining if/when a data use agreement is needed.
  - o The HCSRN Key Contacts directory lists DUA contacts and signatories at each site. These staff can advise on local processes, as needed.
- ✓ The Principal Investigator at each local HCSRN site is responsible for ensuring that appropriate local processes are followed relating to re-identification risk and the need for a data use agreement.
- ✓ Each HCSRN site is responsible for documenting the method and determination of re-identification risk assessment. The HCSRN has developed a checklist for documentation of the expert assessment method for sites to use, if desired.
  - o Specific responsibility for "expert determination" of risk of re-identification varies across HCSRN research centers (e.g. formal consultation with a privacy office representative may or may not be required).
  - o Each investigator is responsible for understanding and following those local requirements. Refer to the HCSRN Key Contacts Directory for DUA staff that can advise on local requirements, if needed.

Data Use Agreements

Additionally, the HCSRN has developed a Data Use Tool Kit (which adheres to federal standards) and data use agreement templates which have been endorsed by the HCSRN's 18 sites' legal departments. Use of these existing tools, as the baseline for developing HSN specific data use agreements will streamline the formal processes necessary prior to any data sharing activities across the HSN and with the CTN.

Sharing of de-identified data from research projects of the HSN node of the CTN:

Completed HSN Projects to Date Include:

CTN-0061
CTN-0065
CTN-0072

The proposed research will include a data sharing plan once final study analyses are completed, drawing on our experience from CTN-0072. The composite limited dataset that will be produced from the proposed research will be maintained behind password-protected firewalls at each of the 10 study sites for future analyses. However, study DUAs will only allow for the disclosure of identifiable data between the participating health systems. Disclosures to other entities will require modifications to those study DUAs or new DUAs between the health systems and said entities. Investigators interested in a dataset that has a variable for sites (de-identified) would need to contact the principal investigator and arrange for that with appropriate DUAs and IRB approvals.

The data sharing plan will include:
A. A description of study design, eligibility and exclusion criteria, data collection procedures, and study measures
B. A plan for creating and sharing a final de-identified dataset including the elements described as above (A.)
C. A data dictionary including variable labels, value labels, allowable ranges, and any applicable details regarding data collection, missing values, etc.

Researchers who would want access to the composite dataset once study analyses are complete will agree to:

- Use these data only for legitimate public-domain research purposes
- Not attempt to identify any individual participants
- Destroy all data when the initially proposed analyses are complete
- Provide the investigator team with copies of all computer code or programs used for analyses in presentations or published papers

Strengths and Limitations

The study has limitations. It is conducted in health systems that are not representative of other health systems and settings. However, these type of health systems have rich EHR data, and serve very large patient populations with considerable diversity. Observational data have inherent weaknesses, lacking information that can introduce confounding and bias. Our methods address these issues by including covariates, using propensity score matching, and by exploring the quality of the data through chart review and external claims data. Even with these weaknesses, the EHR data contain important information on a large number of patients and those data can be used, with recognized limitations, to address important questions for patients with OUD as the opioid crisis continues to evolve. The registry can serve as a resource for the CTN to answer future research questions, to examine patients with co-occurring SUDs, and to use with other data sources. Study methods and algorithms can be shared with other health

systems, such as PBRNs, to expand the registry to more settings with the potential to address a greater variety of research questions. The strengths of the registry can contribute to addressing questions of great importance for clinical care and for patients facing the opioid crisis.

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Appendix A. Health Systems Node sites participating in the proposed Opioid Registry (all of which are also members of the Health Care Systems Research Network http://www.hcsrn.org/en/)

1. Baylor Scott and White Research

Baylor Scott and White (BS&W) supports research on the BS&W Health Plan, serving approximately 200,000 members in 18 counties of Central Texas, including a large rural area. Research is an important part of the S&W mission "to provide personalized, comprehensive, high-quality health care enhanced by medical education and research". Scott & White is 25 miles from the largest active duty military installation in the free world, with a high concentration of military families with specific health concerns.

2. Essentia Institute of Rural Health

Essentia Institute of Rural Health (EIRH) exists to improve the health and health care for the rural population in the United States through research and education. EIRH supports clinical, translational and health services research across the four-state area (Wisconsin, Minnesota, North Dakota and Idaho) served by Essentia Health. Essentia Health's service area includes a rural population of 2 million people.

3. Geisinger Health System Research

Researchers across the clinical enterprise and in Geisinger's research institutes and centers are focused on accelerating discoveries that improve population health, revolutionize the translation of knowledge into practice and create healthcare solutions that are both patient-centered and economically sustainable. We strive to identify ways to best individualize the care of our patients while at the same time developing improved systems of care. Geisinger Health System is a fully integrated health system that serves 31 counties in north-central and northeastern Pennsylvania with 2.6 million residents. The health system service area is one of the oldest and sickest in the nation in terms of co-morbidities and generally serves a rural population.

4. Henry Ford Research Centers & Institutes

Researchers across multiple research centers within Henry Ford Health System (HFHS) participate in the Health Care Systems Research Network. HFHS is an integrated health care system serving more than 800,000 patients and health plan members in Southeast Michigan. Approximately 35% of the HFHS patient population is African American, creating special opportunities for research and quality improvement in the area of health care disparities. https://www.henryford.com/hcp/research

5. Kaiser Permanent Colorado

The Institute for Health Research (IHR) is the research department of Kaiser Permanente Colorado (KPCO), an integrated health care system serving 475,000 members in the Denver-Boulder-Colorado Springs metropolitan area. IHR's mission is to develop, conduct and translate high quality research into practice and to promote evidence-based practices and service-oriented, cost-effective medical care. Working within an integrated delivery system enables IHR investigators and staff to evaluate innovative models of care, conduct epidemiologic and outcomes studies, and participate in clinical trials important to our members and other populations.

6. Kaiser Permanente Mid-Atlantic

Mid-Atlantic Permanente Research Institute (MAPRI) is the research department of Mid-Atlantic Permanente Medical Group, PC, (MAPMG) and Kaiser Permanente Mid-Atlantic States, serving nearly 500,000 patients in Maryland, Virginia, and District of Columbia. MAPRI's mission is to address the clinical, health policy, and service questions perplexing MAPMG providers, our medical program, and the healthcare system, through which we aim to improve the care experience of our patients and communities we serve. MAPRI offers

expertise in health services research, including health disparities and economic impact of healthcare, epidemiology, health information technology, disease specific research in infectious diseases (including HIV/AIDS and hepatitis) and oncology, and clinical trials, all within a racially and ethnically diverse population.

7. Kaiser Permanente Northern California

The Division of Research (DOR) is the research department of Kaiser Permanente Northern California (KPNCal), an integrated healthcare system serving more than 3.4 million members in Sacramento and the Bay Area. DOR research seeks to understand the determinants of illness and well being and to improve the quality and cost-effectiveness of health care for KPNCal members and society at large. The Division of Research offers expertise in health services research, clinical trials, epidemiology, genetics/pharmacogenetics, pharmacoepidemiology, sociology, qualitative research, medical informatics, and quality measurement and improvement.

8. Kaiser Permanente Northwest

The Center for Health Research (TCHR) is a single research center that spans two regions of Kaiser Permanente: Northwest (KPNW) and Hawaii (KPH). TCHR tackles the issues of health and health care from the conceptual to the practical with a multidisciplinary program of public health research within diverse populations.

Center for Health Research-Northwest (CHR-NW) conducts research within KPNW's integrated health care system, which serves about 460,000 members in Northwest Oregon and Southwest Washington. CHR-NW is a multidisciplinary institution whose researchers are experts at using KPNW's comprehensive data systems to conduct research.

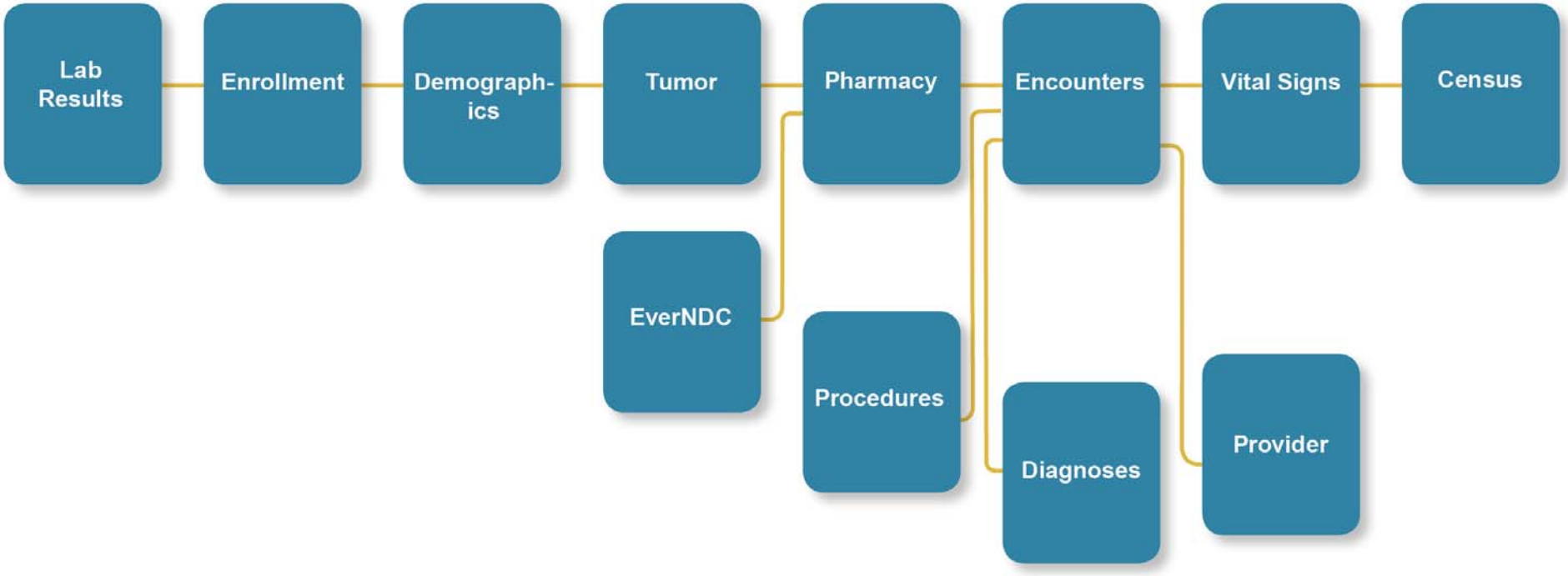
9. Kaiser Permanente Southern California

The Department of Research & Evaluation (R&E) is the research unit of Kaiser Permanente Southern California (KPSCal), an integrated health care system serving more than 3.2 million members in Los Angeles, Orange, San Diego, and surrounding counties. R&E's mission is to initiate and conduct high-quality, innovative public-sector health services, epidemiologic, behavioral, and clinical research that has a demonstrable positive impact on the health and well-being of its members and the general population. The investigators in R&E come from a variety of disciplines and all are dedicated to improving the health of the diverse membership.

10. Meyers Primary Care Institute

Meyers Primary Care Institute (MPCI) is affiliated with Fallon Community Health Plan, which serves 200,000 members throughout Massachusetts, and is consistently rated by US News and World Report as being among the nation's top Medicare and Medicaid Plans. The Institute's mission is to promote primary care practice and population health through innovative research and educational initiatives. MPCI bridges the interests of three sponsoring institutions: Fallon Community Health Plan, Reliant Medical Group, and University of Massachusetts Medical School.

Appendix B: Domains of the Virtual Data Warehouse - Datasource for Registry



Appendix C. Draft opioid registry dataset structure - Table 1

EVERNDC_OPIOID

VARIABLE	DESCRIPTION
DRUG_CODE_TYPE	Type of code used to identify drugs (e.g. "NDC")
GENERIC	Generic name of drug
NDC	National Drug Code

1. List of all opioids that are chosen to be included in the registry
2. NDC codes are the expected codes to be used for identification.
3. The NDC codes that are used at each site may be different. Preliminary analysis will identify those NDC codes that should be included.

EVERNDC_SEDATIVE

VARIABLE	DESCRIPTION
BENZODIAZEPINE	1=BENZODIAZEPINE, 0=OTHER
DRUG_CODE_TYPE	Type of code used to identify drugs (e.g. "NDC")
GENERIC	Generic name of drug
NDC	National Drug Code

1. List of all sedatives that are chosen to be included in the registry
2. NDC codes are the expected codes to be used for identification.
3. The NDC codes that are used at each site may be different. Preliminary

PHARMACY_OPIOID

VARIABLE	DESCRIPTION
MRN	Unique patient ID
NDC	National Drug Code
RXAMT	Number of units dispensed
RXDATE	Date of fill (or order)
RXMD	The provider that prescribed the drug
RXSUP	Days supply

1. Extract all opioid fills 2012-2017
2. One record per fill

OPIOID_COHORT

VARIABLE	DESCRIPTION
MRN	Unique patient ID
MRN_FIRST_OPIOID_FILL	Date of first opioid fill in study period
TUMOR_DXDATE_FIRST	Date of first tumor in VDW tumor file
TUMOR_DXDATE_LAST	Date of most recent tumor in VDW tumor file (not later than 12/31/2017)

1. List of all MRNS that had an opioid fill between 1/1/2012 and 12/31/2017

Draft opioid registry dataset structure - Table 2

DEMOGRAPHICS

VARIABLE	DESCRIPTION
BIRTH_DATE	Birth date
GENDER	Gender
HISPANIC	Days supply
MRN	Unique patient ID
RACE1	Race
RACE2	Race
RACE3	Race
RACE4	Race
RACE5	Race

1. Includes one record per MRN for all MRNs in OPIOID_COHORT

ENROLLMENT

VARIABLE	DESCRIPTION
ENR_END	Stop date of continuous enrollment period
ENR_START	Start date of continuous enrollment period
MRN	Unique patient ID

1. This file has a single record for each enrollment episode for each MRN
2. Use CESR macro to collapse periods. Need to decide on handling of

CENSUS

VARIABLE	DESCRIPTION
GEOCODE	Concatenation of the FIPS codes for State, County, Tract, Block Group, and Block
GEOCODE_BOUNDARY_Y	Census year for which geocode applies
GEOLEVEL	Geographic level of the geocode (B=Block, G=Block Group, T=Tract, Z=Zipcode, U=Unable to be appended, P=if addresss is Post Office box
LATITUDE	Latitude of location
LOC_END	Date on which tenure at this person's location began

LOC_START	Date on which tenure at this person's location ended
LONGITUDE	Longitude of location
MRN	Unique patient ID

1. This file has a single record for each time period in which a person's
2. Extract will be restricted to GEOCODE_BOUNDARY_LEVEL=2010.

It gets complicated when you try to associated census variables like

DEATH

VARIABLE	**DESCRIPTION**
CONFIDENCE	Confidence level of death (E=excellent, F=Fair, P=Poor)
DEATHDT	Date of death
MRN	Unique patient ID

1. Includes one record per death for all MRNs in OPIOID_COHORT

Draft opioid registry dataset structure - Table 3

UTILIZATION

VARIABLE	DESCRIPTION
ADATE	Admission date of encounter
DDATE	Discharge date of the encounter
DEPT	The department (in 6 char code) where the encounter took place as documented in the source data. This is not necessarily the specialty of the clinician providing services.
ENC_ID	Unique identifier for each encounter record
ENCTYPE	Type of Patient Encounter
ENCOUNTER_SUBTYPE	Subtype of encounter
FACILITY_CODE	Local Facility code that identifies hospital or clinic.
MRN	Unique patient ID
PROVIDER	Provider code for the provider who is most responsible for this encounter.Usually physician, nurse practitioner, physician assistant, optometrist, etc.Use Same coding scheme as RXMD in RX table. For encounters with multiple providers and there isn't a clear one in charge, please choose one arbitrarily so the encounter can be linked to the diagnosis and procedure files.

1. Includes one record per encounter for all MRNs in OPIOID_COHORT
2. The following ENCTYPEs are excluded: LO (lab only), RO (radiology only), EM (email)
3. Records for and MRN are only included if ADATE is >= (MRN_FIRST_OPIOID_FILL_DT-360)

Draft opioid registry dataset structure - Table 4

DIAGNOSIS

VARIABLE	**DESCRIPTION**
ADATE	Admission date of encounter
DIAGPROVIDER	Provider who made the Diagosis.
DX	The International Classification of Diseases Code
DX_CODETYPE	Code type flag ("09" OR "10")
ENC_ID	Unique identifier for each encounter record
ENCTYPE	Type of Patient Encounter
MRN	Unique patient ID
PRINCIPAL_DX	reason why the patient was admitted to the hospital for care. This is the diagnosis on which the DRG is based. Note that the principal diagnosis is very different from the admitting diagnosis which is assigned at the beginning of the stay. For example, if a patient was admitted to a hospital with an admitting diagnosis of chest pain which was later diagnosed as a heart attack during the stay, the principal diagnosis would be heart
PRIMARY_DX	Primary diagnosis is the illness or injury that was the most serious/severe/life-threatening and/or resource intensive. From a claims perspective, it is the main reason for a provider's services being rendered (and billed/paid for). Specify primary diagnosis as defined by the site's institutional source data. For an outpatient encounter, it is expected that there should be one and only one primary diagnosis. For an inpatient stay, there can be multiple primary diagnoses, one for each provider claim during the stay. A provider may have multiple claims during a stay, each with a primary diagnosis. If multiple bills were submitted for a claim, choose the final/last professional bill. For claims systems, the primary diagnosis may be found in the HCFA professional bill (field number 21.1 in the HCFA 1500 or "2400 SV107-1" in the electronic form) which is the first diagnosis code listed. The other diagnoses on this bill should be identified as "S" (Secondary Dx). The values "P" (Primary Dx) and "S" (Secondary Dx) should only be specified for encounters where there's a clearly defined primary diagnosis in the source data. Thus, if the source data does not identify primary or secondary diagnosis for a specific encounter, then set all diagnoses for that encounter to "X" (Not Classifiable). If all diagnoses for an encounter are reported as secondary in the source data, then set primary_dx="S" (secondary). Multiple primary diagnoses are allowed if the final/last professional claim can't be determined using the criteria above or if the primary diagnosis was a local combination code that has to be put into multiple records to have values within a standard coding system.

PROVIDER	Provider code for the provider who is most responsible for this encounter.Usually physician, nurse practitioner, physician assistant, optometrist, etc.Use Same coding scheme as RXMD in RX table. For encounters with multiple providers and there isn't a clear one in charge, please choose one arbitrarily so the encounter can be linked to the diagnosis and procedure files.

1. Includes one record per diagnosis for all MRNs in OPIOID_COHORT
2. The following ENCTYPEs are excluded: LO (lab only), RO (radiology only), EM (email)
3. Records for and MRN are only included if ADATE is >= (MRN_FIRST_OPIOID_FILL_DT-360)

Draft opioid registry dataset structure - Table 5

PROCEDURE

VARIABLE	DESCRIPTION
ADATE	Admission date of encounter
CPTMOD1	CPT Modifier Code 1 as found in the source data
CPTMOD2	CPT Modifier Code 2 as found in the source data
CPTMOD3	CPT Modifier Code 3 as found in the source data
ENC_ID	Unique identifier for each encounter record
ENCTYPE	Type of Patient Encounter
MRN	Unique patient ID
PERFORMING_PROVIDER	
PROCDATE	
PX	Procedure code.Depending upon the type of Procedure the following is the format of the Procedure Codes : #### --> ICD9, ##### --> CPT4, A#### --> HCPCS, ### for Revenue Codes # = Numeric Digit, A=Alphabet Letter Convertion of local codes to standard codes when possible. Decimal point rule for ICD9s: if there are two or fewer characters, there is no decimal point If th than two, the point goes between the second and third characters. If conversion of a local code to a standard code is not possible, this colulm will have a missing value, even though there is a non-missing value in origPx
PX_CODETYPE	09 ICD9 C4 CPT4 H4 HCPCS RV Revenue code LO Local homegrown OT Other
PXCNT	Number of times the procedure was performed during the encounter

1. Includes one record per procedure for all MRNs in OPIOID_COHORT
2. The following ENCTYPEs are excluded: LO (lab only), RO (radiology only), EM (email)
3. Records for and MRN are only included if ADATE is >= (MRN_FIRST_OPIOID_FILL_DT-360)

Draft opioid registry dataset structure - Table 6

PHARMACY_SEDATIVE

VARIABLE	DESCRIPTION
MRN	Unique patient ID
NDC	National Drug Code
RXAMT	Number of units dispensed
RXDATE	Date of fill (or order)
RXMD	The provider that prescribed the drug
RXSUP	Days supply

1. Extract all sedative fills 2012-2017 for MRNs in OPIOID_COHORT
2. One record per fill

PROVIDER_SPECIALTY

VARIABLE	DESCRIPTION
PROVIDER	Unique identifier of provider
PROVIDER_BIRTH_YEAR	Provider year of birth
PROVIDER_GENDER	Provider gender
PROVIDER_HISPANIC	"Y"=Provider is Hispanic
PROVIDER_RACE	Provider race
PROVIDER_YEAR_GRADU	Year provider graduated medical/technical/nursing school
SPECIALTY_DESCRIPTION	Description of specialty #1
SPECIALTY2_DESCRIPTION	Description of specialty #2
SPECIALTY3_DESCRIPTION	Description of specialty #3

1. Extract provider specialty information for all providers in system

PERSON_TIME_DENOM

VARIABLE	DESCRIPTION
AGE_YEAR	Year of age, starting at 19
GENDER	Gender
MEMBER_MONTHS	Member months in this month
MONTH	Month of the year (1 to 12)
MONTH_DATE_START	First day of this calendar month (e.g., 01MAR2015).
MONTH_DATE_STOP	Last day of this calendar month (e.g., 31MAR2015).

RACE	Race (derived)
YEAR	Year (2012 to 2017)

1. This is a dataset created by joining the VDW enrollment and
2. The following ENCTYPEs are excluded: LO (lab only), RO (radiology
3. Will need to decide on a race classification derivable from the VDW

Derived dataset

OPIOID_USE_MONTH

MRN	Unique patient ID
FILLS_COUNT	Number of opioid fills in this month
ME_FILLED	Morphine equivalent milligrams for fills in this month
ME_USED	Morphine equivalent milligrams inferred to have been used in this month
MONTH	Month of the year (1 to 12)
MONTH_DATE_START	First day of this calendar month (e.g., 01MAR2015).
MONTH_DATE_STOP	Last day of this calendar month (e.g., 31MAR2015).
MRN	Unique patient ID
RXSUP	Days supply of fills in this month
RXAMT	Quantity (e.g., number of pills) dispensed in this month
YEAR	Year (2012 to 2017)

1. Includes summary of opioid fill data by month, and the inferred morphine equivalent milligrams presumed to have been
2. Should this be a "permanent" dataset in the registry, or created when needed?
3. My approach to determining monthly use first creates daily records. But we may prefer to use the simpler

Appendix D. Opioid analgesic medication included in registry.[a]

Generic drug name	Morphine equivalent conversion factor[b]
Codeine	0.15
Dyhidrocodeine	0.25
Fentanyl (patch)[c]	7.20
Fentanyl (spray)	0.125
Fentanyl citrate	0.125
Hydrocodone	1.00
Hydromorphone	4.00
Hydromorphone HCL (suppository)	6.67
Levorphanol tartrate	11.00
Meperidine	0.10
Methadone	3.00
Morphine	1.00
Oxycodone	1.50
Oxymorphone	3.00
Oxymorphone (suppository)	10.00
Pentazocine/acetaminophen	0.37
Propoxyphene HCL	0.23
Tramadol	0.10