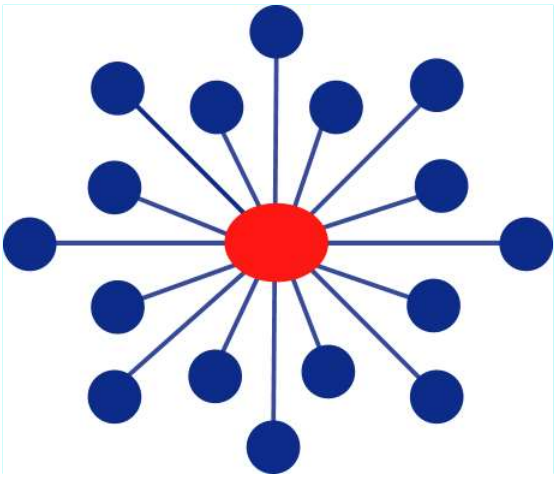

NIDA CTN Protocol 0095

Clinic-Randomized Trial of Clinical Decision Support for Opioid Use Disorders in Medical Settings (COMPUTE 2.0)

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Funded by: National Institute on Drug Abuse (NIDA)

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
BPA	Best Practice Advisory
CCC	Clinical Coordinating Center
CCTN	Center for the Clinical Trials Network
CDS	Clinical Decision Support
CFR	Code of Federal Regulations
CMS	Centers for Medicare and Medicaid Services
CoC	Certificate of Confidentiality
CRF	Case Report Form
CTN	Clinical Trials Network
DSC	Data and Statistics Center
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DSMB	Data Safety Monitoring Board
ED	Emergency Department
EHR	Electronic Health Record
ERC	Ethics Review Committee
FTE	Full-Time Equivalent
FWA	Federal wide Assurance
GCP	Good Clinical Practice
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HPMG	HealthPartners Medical Group
HSP	Human Subjects Protection
ICD-10	International Classification of Diseases, 10th Revision
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
IT	Information Technology
MAT	Medication Assisted Treatment
MD	Medical Doctor
MOUD	Medications for Opioid Use Disorder
NHLB	National Heart Lung and Blood Institute
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NP	Nurse Practitioner
OHRP	Office for Human Research Protection
OUD	Opioid Use Disorder
PA	Physician Assistant
PCP	Primary Care Provider
PI	Principal Investigator
PNMG	Park Nicollet Medical Group
QA	Quality Assurance

Abbreviation	Definition
RE-AIM	Reach, Effectiveness, Adoption, Implementation, Maintenance
RN	Registered Nurse
RVU	Relative Value Units
SMI	Serious Mental Illness
TAPS	Tobacco, Alcohol, Prescription Medication and other Substance use
TCRRVs	Total Care Relative Resource Values ™
UC	Usual Care
XR-NTX	Extended-Release Injectable Naltrexone

2.0 STUDY SYNOPSIS

2.1 Study Objectives

Objective: Through CTN-0076-Ot (Clinical Decision Support for Opioid Use Disorders in Medical Settings: Pilot Usability Testing in an EMR (COMPUTE)), our team has iteratively developed and piloted a web-based and electronic health record (EHR)-integrated Opioid Use Disorder (OUD) Clinical Decision Support (CDS) system to offer expert guidance to primary care providers (PCPs) on the diagnosis and management of OUD. The OUD-CDS has been implemented within the EPIC EHR of one large care system and was piloted with 55 providers to ensure content validity and provider satisfaction. Our team will now implement this OUD-CDS in a large multi-site clinic-randomized controlled trial to evaluate its impact on practice process measures and patient outcomes. We also aim to prepare for scalability (i.e., integration into usual primary care practice after the study is complete) and dissemination by evaluating facilitators and barriers to implementation, determining the costs of implementation and maintenance, and assessing the short-term cost impacts of the OUD-CDS.

Definitions

Intervention Period
- Varies by system
- OUD-CDS implementation date through a predetermined time at which the Wizard interfaces will be turned off in the intervention clinics

Accrual Period
- Varies by system
- OUD-CDS implementation date through a predetermined time at which no more people will be included in the analytic sample

Index Date
- Varies by patient
- First visit at which the OUD-CDS identifies that the patient is study eligible

Observation Period
- Varies by patient
- Index visit date through a predetermined time at which outcome data will no longer be accumulated

The study will include three large diverse care systems and randomize a minimum of 30 clinics to receive the OUD-CDS intervention or usual care (UC). In intervention clinics, the OUD-CDS will identify patients who are at high risk for OUD or diagnosed with OUD; use data stored in the EHR for each eligible patient to assemble treatment recommendations tailored to each patient's current needs; display these recommendations to PCPs via the OUD-CDS user interface; and store analytic data from all targeted visits. In UC clinics, the OUD-CDS will run invisibly in the background to identify high-risk or OUD patients, assemble treatment recommendations tailored to each eligible patient's needs, and store analytic data from all targeted visits.

Specific Aims:

Aim 1. To implement OUD CDS in primary care settings and assess its impact on process measures related to diagnosis of patients at high risk for OUD, as well as prescription of naloxone for patients at high risk for or diagnosed with OUD.

H1.1: Patients previously undiagnosed with OUD but identified as high risk by the OUD-CDS at an index visit will be more likely to receive an OUD diagnosis (in the problem list or as an International Classification of Diseases, 10th Revision (ICD-10) visit code) in intervention clinics than in UC clinics within 30 days post-index.

H1.2: Patients previously diagnosed with OUD or identified as high risk by the OUD-CDS at an index visit will be more likely to have naloxone rescue kits ordered in the intervention clinics than in the UC clinics within 30 days post-index.

Aim 2. To assess the impact of OUD-CDS on important patient outcomes of initiation and maintenance of Medications for Opioid Use Disorder (MOUD) in patients identified as having OUD or being at high risk for OUD.

H2.1: Patients identified as having OUD or as being at high-risk for OUD by the OUD-CDS at an index visit will be more likely to have MOUD orders or referral for OUD treatment within 30 days post-index in intervention clinics than in UC clinics.

H2.2: Patients identified as having OUD or as being at high-risk for OUD by the OUD-CDS at an index visit will have significantly more days covered by a MOUD prescription at 90 days post-index in intervention clinics than in UC clinics.

Aim 3. To assess the long-term impact of OUD CDS on important patient outcomes in patients with OUD or identified as high risk for OUD.

H3.1: Patients with OUD or identified as high-risk for OUD by the OUD-CDS who are cared for in intervention clinics will have significantly fewer post-index emergency department (ED) visits during the observation period (i.e., the period between each patient's index date and last observation) compared to patients cared for in UC clinics.

H3.2: Patients with OUD or identified as high-risk for OUD by the OUD-CDS who are cared for in intervention clinics will have significantly fewer post-index hospitalizations during the observation period compared to patients cared for in UC clinics.

Aim 4. To describe and quantify costs of OUD-CDS implementation and maintenance and the short-term cost impacts of the OUD-CDS.

H4.1: After controlling for demographics, baseline clinical status and prior costs of care, patients with OUD or identified as high risk for OUD by the OUD-CDS will have lower healthcare costs in intervention compared to UC clinics during the observation period (i.e., savings from lower ED visits and hospitalizations will outweigh increased costs of OUD treatment and naloxone rescue kits and OUD-CDS implementation and maintenance).

Aim 5. To use mixed quantitative and qualitative methods to identify, describe and quantify barriers and facilitators to implementation of the OUD-CDS so that it can be adapted to maximize its use and effectiveness.

Secondary Analyses: As secondary outcomes, we may assess whether patients with OUD or identified as high risk for OUD by the OUD-CDS who are cared for in intervention clinics have lower post-index rates of all cause death and of fatal or non-fatal opioid overdoses during the intervention period compared to similar patients in UC clinics. We will also assess OUD-CDS use rates for intervention clinics and assess whether the effectiveness of OUD-CDS varies as a function of site, clinic, provider or patient characteristics. Finally, we will assess whether PCP ratings of confidence in treating patients with OUD differ at 9 months between treatment groups, and how intervention PCPs rate satisfaction and acceptability of the OUD-CDS tool at 9 months.

Exploratory Analyses: In exploratory analyses, we will assess whether (a) PCPs in intervention clinics who are non-waivered at go-live dates are more likely to become buprenorphine-waivered than PCPs in UC clinics during the intervention period; (b) waivered PCPs in intervention clinics are more likely to prescribe buprenorphine than PCPs in UC clinics during the intervention period; (c) whether PCPs in intervention clinics who are non-waivered at go-live dates are reportedly more likely to prescribe buprenorphine should a waiver no longer be required than PCPs in UC clinics measured prior to go-live dates and at 9 months following go-live dates; (d) if we have adequate data, potentially via health plan or Surescripts data, whether adherence/persistence to methadone, buprenorphine, XR-NTX or therapy for patients with OUD differs for patients in intervention vs. UC clinics during the observation period; and (e) PCPs in intervention clinics are more likely to screen their patients for mental health conditions and infectious diseases than PCPs in UC clinics during the intervention period.

Notes: The COVID-19 pandemic has delayed implementation, and these impacts to date are reflected in the updated timeline (Section 7.2). HealthPartners vanguard clinic sites went live on February 3, 2021; and remaining randomized clinics went live on April 7, 2021. The vanguard clinic site at Geisinger is anticipated to go live in November 2021, with remaining sites anticipated to be operational in December 2021 or January 2022. The vanguard clinic site at Essentia is anticipated to go live in January 2022, with remaining sites anticipated to be operational by April 2022.

Two supplemental studies are associated with this study and will be conducted only at HealthPartners. The first, 3UG1DA040316-06S3 (aka CTN-0095-A-1), is a cluster-randomized trial that randomizes half of COMPUTE intervention clinics to receive decision support aimed at suicide prevention. The second, 3UG1DA040316-06S4 (aka CTN-0095-A-2), is a clinician-randomized trial of an intervention aimed at reducing OUD stigma for PCPs. Separate protocols for each supplemental application reference this protocol.

2.2 Study Design and Outcomes

In this multicenter clinic-randomized pragmatic trial, clinics will be randomized 1:1 to OUD-CDS or to UC within each healthcare system. To encourage a larger number of buprenorphine-waivered PCPs in both intervention and UC clinics, we may offer financial incentives to become waivered.

Primary outcome measures will include:

1. OUD diagnosis (in the problem list or as an ICD-10 visit code) within 30 days of index visit for patients identified by the OUD-CDS as being at high risk of OUD
2. Naloxone prescription within 30 days of index visit for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
3. MOUD orders or referral to OUD treatment within 30 days of index visit for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
4. Total days covered by an MOUD prescription in the 90 days after index visit for patients with OUD or identified by the OUD-CDS as being at high risk for OUD

Secondary outcome measures will include:

1. OUD diagnosis (in the problem list or as an ICD-10 visit code) at index or within 90 days of index visit for patients identified by the OUD-CDS as being at high risk of OUD
2. Naloxone prescription at index or within 90 days of index visit for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
3. MOUD orders or referral to OUD treatment at index or within 90 days of index visit for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
4. Number of ED visits during the observation period for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
5. Number of hospitalizations during the observation period for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
6. Healthcare costs during the observation period for patients with OUD or identified by the OUD-CDS as being at high risk for OUD, compared with healthcare costs over the same interval preceding the observation period
7. Cost of OUD-CDS implementation and maintenance
8. All-cause mortality rates during the observation period for patients at high risk of OUD
9. Fatal and non-fatal opioid overdoses during the observation period for patients at high risk of OUD
10. Rates of OUD-CDS use in intervention clinics
11. PCP ratings of confidence in treating patients with OUD at baseline and 9 months
12. Intervention clinic PCP ratings of satisfaction and acceptability of the OUD-CDS at 9 months

Other outcome variables will include:

1. Number of non-waivered PCPs becoming buprenorphine waivered during the intervention period, assessed via health system administrative data
2. Number of buprenorphine prescriptions written by waivered PCPs during the intervention period
3. PCP ratings of likelihood to prescribe buprenorphine for patients with OUD, should no waiver be required, measured prior to go-live dates and at 9-months following go-live dates
4. Adherence to therapy during the observation period, assessed via Clarity and claims data
5. Number of patients diagnosed with OUD screened for mental health comorbidities and infectious diseases during the observation period

2.3 Sample Size and Study Population

The study will be conducted at a minimum of 30 primary care clinics within 3 healthcare systems in the United States that are geographically dispersed and will include a racially, ethnically and socioeconomically diverse population. Clinics will be randomized equally within each care system and balanced on pre-randomization outcomes, such as the percentage of patients at high-risk or with diagnosed OUD, and on clinic characteristics that may enhance or impede intervention uptake and adherence, such as the number of buprenorphine-waivered PCPs (see **Section 10.2**). PCPs who practice at randomized clinics will be asked to complete pre-and post-implementation surveys assessing their comfort and confidence treating patients with OUD. Primary and secondary outcomes data will be collected from the EHR or CDS tool for each patient with an

eligible index visit. Following intent-to-treat principles, all PCPs and eligible patients will be attributed to the arm to which their clinic is randomly assigned. Surveys will also ask providers in intervention clinics about their perceptions of the OUD-CDS. Additionally, we will conduct surveys with patients and interviews with PCPs, clinic staff, clinic leaders and patients to understand their perceptions of the acceptability of OUD treatment in primary care and their impressions of the OUD-CDS to help improve the implementation and uptake of the OUD-CDS.

2.4 Treatment/Assessment/Intervention and Duration

The OUD-CDS provides clinical guidance to PCPs in the screening, diagnosis and treatment of OUD, along with common comorbid conditions, and will display for patients with OUD or at high risk for OUD in intervention primary care clinics during each site's intervention period (see timeline). PCPs are also able to access the OUD-CDS in EPIC for patient encounters for which it did not display (e.g., new patient visits). Patient follow-up time from the date of index visit is estimated to range from 18 to 31 months.

The OUD-CDS will be tested and evaluated prior to implementation, in the early implementation phase, and during the maintenance phase at each site by a combination of qualitative data collection, monitoring of use rates and PCP surveys at all time points.

2.5 Safety Reporting

This study will randomize clinics to receive or not receive a CDS tool to facilitate the provision or accepted standards of care. With this work, we are not attempting to change the standard of care for OUD treatment in primary care, but rather are attempting to help PCPs achieve this standard of care in OUD treatment. PCPs will be trained that, as with other clinical decision tools, the OUD-CDS is meant to supplement but not supersede clinical judgment. PCPs will be able to choose to follow or to not follow the guidance of the CDS at any given time for any given patient. PCPs will be asked to use the Feedback Tab within the tool to let the team know of questions or potential errors in the CDS. Additionally, PCPs will be trained to let the research team know via the Feedback Tab when their clinical judgment is inconsistent with the CDS. This feedback will be monitored by the treatment team and the CDS algorithms adjusted if indicated.

An independent Clinical Trials Network (CTN) Data and Safety Monitoring Board (DSMB) will monitor this study. Tables will summarize, by site and blinded treatment group, (a) number of patients, index visits and eligible clinic encounters during the intervention period; (b) rates of OUD-CDS use in intervention clinics; (c) baseline clinic and patient characteristics; and (d) safety measures (overdose rates, hospitalization rates, ED visit rates, content of PCP feedback via Feedback Tab and any actions taken in response). Reports will be provided to the DSMB at a frequency the DSMB requests. The CTN DSMB will be responsible for conducting periodic reviews of accumulating study data. The CTN DSMB will provide an opinion on whether there is support for continuation of the trial, evidence that study procedures should be changed, or evidence that the trial should be halted for any reason, such as the safety of study participants, the efficacy of the treatment under study or inadequate trial performance.

2.6 Analyses

Aims 1 through 3 pertain to the effectiveness of the OUD-CDS intervention relative to UC, predicting that it will increase diagnosis, naloxone prescribing, and access to MOUD, and

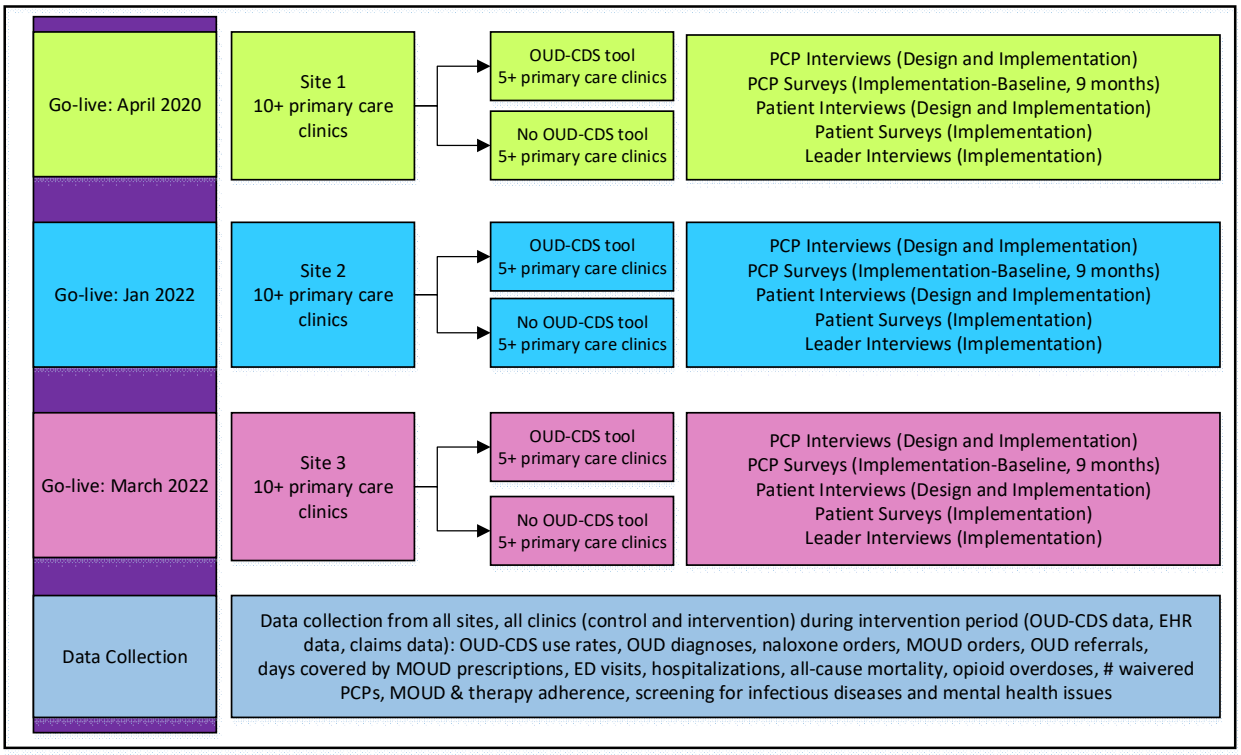
decrease ED visits and inpatient hospital stays. These hypotheses will be tested using generalized linear mixed models to account for clustering of outcomes within eligible patients and randomized clinics or generalized estimating equations to compare event rates across clinics. Outcomes will be normalized via distribution-appropriate link functions (e.g., logistic-Normal, Poisson-Normal). Clinic-randomized treatment group, care system and other predictors will be treated as fixed effects.

For Aim 4, OUD-CDS implementation and maintenance costs will include programming, training and ongoing algorithm maintenance but exclude research costs, using micro-cost accounting methods and nationally-representative pricing of inputs. A generalized linear model, allowing clustering by clinic and controlling for demographics and baseline clinical risk factors, will estimate costs by study arm to account for the skewed distribution of costs.[1-3] Economic analyses will be done in consultation with the NIDA P-30 CHERISH program.

The Aim 5 mixed methods analysis will include an iterative, team-based, triangulation of quantitative and qualitative data sources. Qualitative analysis of the field notes, observations and interviews will be conducted using techniques of qualitative content analysis based on a deductive-directed approach to evaluate the factors influencing RE-AIM constructs.[4]

3.0 STUDY SCHEMA

Overview of COMPUTE 2.0: (Note: go-live and intervention periods have been impacted by delays due to COVID-19. Please refer to **Section 7.2** Study Timeline.)



3.1 Key Research Site Roles

Prime Healthcare System: HealthPartners
- Co-Lead and Site Principal Investigator (MD, DO, PhD)
- Co-Investigator
- Health Economist
- Biostatistician
- Clinical Champion (MD, PhD, NP, PA, DO)
- Project Manager
- Research Assistant
- EPIC Programmer
- Web Programmer
- User Experience Expert
- Data/Clarity Programmer
- Mixed Methods Consultant

Partner Healthcare Systems (Geisinger and Essentia):
- Site Principal Investigator (MD, DO, PhD)
- Co-Investigator with mixed methods experience
- Clinical Champion (MD, PhD, NP, PA, DO)
- Research Coordinator/Project Manager
- EPIC Programmer
- Data/Clarity Programmer

4.0 INTRODUCTION

4.1 Background and Significance to the Field

Statement of the Problem. We are in the midst of an opioid epidemic.[5] More than 72,000 people in the US died from drug overdoses in 2017, including illicit and prescription opioids.[6] Approximately 20% of patients diagnosed with OUD seek treatment, but only 25% of those receive MOUD.[7] Primary care is the most common point of healthcare contact in the US and may be able to help reduce this significant treatment gap. Buprenorphine and monthly injections of XR-NTX show promise for OUD treatment in primary care.[8-14] Over 50,000 physicians are waivered to prescribe buprenorphine, but only 14,000 (28%) do.[15] Providers identify time constraints, poor access to clinical guidelines, and lack of institutional support, staff training and confidence as barriers to using buprenorphine.[15-18] Similar barriers limit the use of XR-NTX.[19]

In the last decade, EHR-linked web-based point-of-care CDS systems designed to improve quality of chronic disease care have become increasingly sophisticated and successful [20-22]. Our team has developed a CDS system that improves glucose and blood pressure control in adults with diabetes, reduces 10-year cardiovascular risk in high risk patients, and increases recognition of adolescents with hypertension in clinic-randomized trials. [23-27] Use rates of the CDS system remain high at 70-80% of targeted encounters, and the CDS tools have obtained 95% PCP satisfaction ratings. This web-based CDS system is designed for scalability, is used by 4 large health care systems serving approximately 2 million patients and has recently been implemented through a National Heart, Lung, and Blood Institute (NHLBI) grant at 60 federally health care qualified centers in 10 states.

Prior Work. Through CTN-0076-Ot, we piloted a CDS tool that supports the diagnosis and treatment of OUD in primary care at HealthPartners. A total of 55 enrolled PCPs included 8 of our 11 buprenorphine-waivered MDs, 24 non-waivered medical doctors (MDs), and 22 non-waivered advanced practice PCPs. The OUD-CDS tool translates the NIDA CTN Blending Initiative White Paper [unpublished] into web-based algorithms that identify patients at high risk for OUD and provides a usable and intuitive interface that guides PCPs through OUD management and referrals, when indicated. The OUD-CDS tool links to the prescription drug monitoring database. It uses the Tobacco, Alcohol, Prescription medication and Substance Use (TAPS) tool [28] to screen patients for OUD and prompts use of Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) [29] diagnostic criteria for patients with positive TAPS screens. Next, the treatment selection module alerts PCPs to any relative contraindications to certain MOUDs, and guides prescription of MOUDs or referral for OUD treatment, as appropriate. It provides patient educational materials, including a one-page summary of MOUDs, as well as detailed MOUD-specific handouts. The final module prompts screening for common comorbidities, such as infectious diseases and mental health conditions, and includes recommendations to bring vaccinations up-to-date. All modules contain active guidelines that make it easy to order recommended labs, medications and referrals by clicking on links within the text, saving the PCP time and clicks. The orders are then reviewed within the EHR prior to signing.

In CTN 0076-Ot, use rates were disappointingly low, in that PCPs used the OUD-CDS in 5% of eligible encounters with patients identified at high risk. PCPs reported that barriers to use included not seeing the alert banner in EPIC, not feeling they had enough time to address opioid risk, or

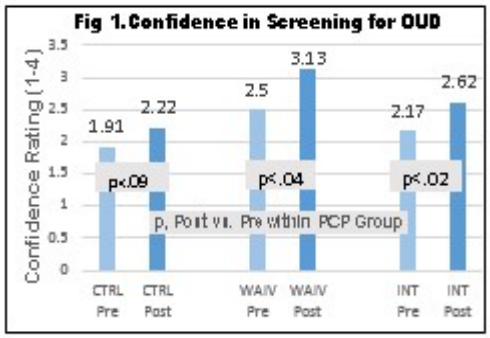
feeling OUD was a low priority for the patient or that the PCP could tell who was at risk for OUD. This PCP feedback has been instrumental in our planning for this trial, as it gives us actionable steps to take to improve use rates of the OUD-CDS, which we outline in **Section 8.5 (Strategies for Recruitment and Retention)**. One key change in the larger study will be to have multiple alerts to the care team that a patient has been identified as high risk and that use of the OUD-CDS is recommended, including alerts to the rooming staff. In prior work, this has substantially improved uptake of the CDS tool.

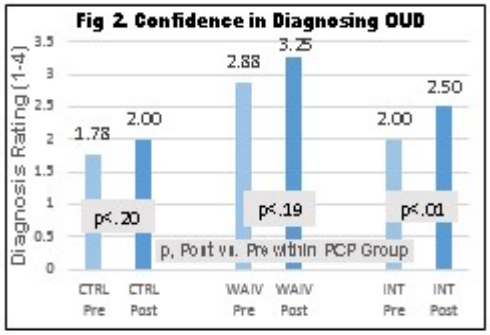
In surveys, 66% of intervention PCPs (21 of 32 PCPs) and 75% of waivered intervention PCPs (6 of 8 PCPs) were moderately or very likely to recommend the tool to colleagues. In all, 89% of PCPs thought the OUD-CDS helped them screen for OUD, 86% felt the tool made them feel more comfortable in prescribing MOUDs, 93% felt the tool made it easier to discuss treatment options with patients, 93% felt the tool helped them know when to refer patients, and 82% felt the tool saved them time.

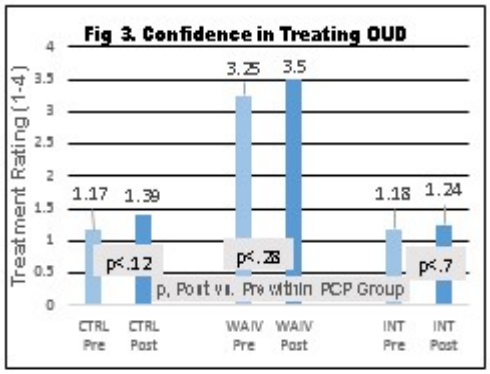
Intervention PCPs (both waivered and non-waivered) reported increased confidence in screening for OUD after the intervention on 4-point Likert scales (Figure 1), while only non-waivered PCPs saw a significant increase in confidence in diagnosing OUD by the end of the trial (Figure 2). None of the PCPs reported a significant increase in treating OUD by the end of the trial (Figure 3).

Early feedback from the COMPUTE 1.0 pilot has informed research strategies to further improve uptake of the tool and the user experience, such as considering use of other care opportunities (e.g., telephone encounters where opioid prescription renewals are requested; annual renewal of opioid use agreements), involving rooming staff in the screening process, changing the type of EHR alert, and simplifying the user interface. We will incorporate these changes in COMPUTE 2.0 as detailed in **Section 8.5**, as well as provide clinic- and PCP-specific use rates to clinic leadership, which in prior work has increased use rates to 70-80% of eligible encounters.[30]

Figures 1-3. PCP Confidence in Screening, Diagnosing and Treating Patients with OUD







Summary of Study Design. The proposed study will include 3 large diverse healthcare systems and randomize a minimum of 30 clinics equally within each system to receive the OUD-CDS intervention or UC. In intervention and UC clinics, the OUD-CDS will identify study-eligible patients, those who are at high risk for OUD or diagnosed with OUD; and will use data stored in the EHR to assemble treatment recommendations tailored to the needs of each study-eligible patient. In intervention clinics, these treatment recommendations will be displayed via the OUD-CDS user interface. Finally, data from all targeted visits in all randomized clinics will be stored in a data repository for analysis and reporting needs. The targeted visits for each study-eligible

patient in all randomized clinics will be the index visit, the first visit at which the OUD-CDS identifies that the patient is study eligible, and all post-index visits through the end of the intervention period, regardless of continued eligibility. This pragmatic cluster-randomized design is the optimal design to effectively and efficiently implement this tool in primary care clinics while protecting against study contamination and allowing for collection of process and outcome data at UC clinics.

Statement of Hypotheses. We hypothesize that patients at high-risk for OUD in intervention clinics will be more likely to be diagnosed with OUD, and that those at high-risk for or diagnosed with OUD will be more likely to receive naloxone rescue kits, have MOUD orders or referrals, have more days covered by MOUD prescriptions, have fewer ED visits and hospitalizations, and have lower healthcare costs. We hypothesize that qualitative data will help to identify barriers and facilitators to implementation and propose steps to mitigate barriers.

Mixed Methods Approach. Virtually every evidence-based intervention in medicine has turned out to be difficult to implement and maintain in real life practice and to fall far short of fidelity to the process used in randomized trials.[31, 32] As a result, a whole new field of dissemination and implementation research has been developing over the last 20 years. These studies have now gone well beyond the previous paradigm of focusing on changing the attitudes and behaviors of individual physicians to a growing awareness that the need instead is to alter the environment in which physicians work so that it is easier to do the desired evidence-based thing than to stick with old established habit patterns.[33] That means focusing change efforts on organizational factors and practice systems. The Solberg conceptual framework has proven to be particularly helpful in clarifying this new approach.[34]

Simultaneously, there has been increasing interest in transitioning effectiveness clinical trials from traditionally highly selective and controlled circumstances to pragmatic trials that make use of normal care delivery processes and patients.[35] The measurement of such trials has been facilitated by the development of a conceptual framework called RE-AIM, an acronym for 5 key facets of such studies – Reach, Effectiveness, Adoption, Implementation, and Maintenance.[36, 37] Recently, the developers of RE-AIM have recognized the need for more flexible use of this framework, greater use of qualitative methods to understand why interventions are not used consistently, and making adaptations in the implementation approach based on such understandings.[38-41] We propose to use the RE-AIM framework to guide (1) a monitoring system for intervention problems, (2) a mixed methods evaluation of the reasons for those problems, and (3) modification of the intervention to reduce those problems. These steps will be reiterated in a cyclic fashion, resulting in a more sophisticated approach to the long-standing quality improvement emphasis on Plan-Do-Study-Act rapid cycle tests of change.[42, 43] Furthermore, we will take advantage of the staggered implementation of the study through three different care systems to ensure that the solutions for intervention problems in Site 1 are not assumed to be the same as the approach in subsequent sites without further RE-AIM monitoring and evaluation.

Potential Risks and Benefits. There is a small but important risk that the OUD-CDS could provide the wrong treatment advice at the wrong time. As with other clinical decision tools, the OUD-CDS makes suggestions for patient care that are meant to supplement but not supersede clinical judgment. PCPs can choose to follow or not follow the guidance of the CDS at any given

time in any given patient encounter. PCPs will be trained to let the research team know via the Feedback Tab in the CDS when their clinical judgment leads them to a different action than that suggested by the CDS. These events will be monitored in real time by the treatment team and the CDS algorithms adjusted if there are found to be errors. Every clinical encounter requires medical judgment and poses some element of risk to patients. In the situation of a PCP who is unfamiliar or uncomfortable with OUD, use of the CDS will likely make care safer by providing suggestions to screen and assess for OUD using validated tools, and to encourage referrals when patients are classified as high risk. We will not be encouraging buprenorphine use in non-certified providers, and this will be reinforced in PCP training on the CDS. For buprenorphine-certified providers, the use of the CDS may improve the likelihood of using MOUD in high-risk situations; however, the risks of MOUD are generally considered lower than untreated OUD in high-risk situations. This is a minimal risk study and the risk to a patient who is not receiving MOUD greatly exceeds the risk of the CDS intervention. Overall, the potential benefits of providing the OUD-CDS to intervention clinics, which include the ability to improve the identification of patients at-risk for OUD, to guide screening and diagnosis of OUD, and to guide treatment selection and prescription of MOUDs or referrals for people with OUD, ultimately increasing access to OUD treatment for patients with OUD in primary care, outweigh the potential risks outlined above.

5.0 OBJECTIVES

5.1 Primary Objectives

The **overarching aim of this study** is to implement this OUD-CDS in a large multi-site clinic-randomized controlled trial to evaluate its impact on practice process measures and patient outcomes in at least 30 primary care clinics across three healthcare systems.

Specific Aims:

Aim 1. To implement OUD CDS in primary care settings and assess its impact on process measures related to diagnosis of patients at high risk for OUD, as well as prescription of naloxone for patients at high risk for or diagnosed with OUD.

H1.1: Patients previously undiagnosed with OUD but identified as high risk by the OUD-CDS at an index visit will be more likely to receive an OUD diagnosis (in the problem list or as an ICD-10 visit code) in intervention clinics than in UC clinics within 30 days post-index.

H1.2: Patients previously diagnosed with OUD or identified as high risk by the OUD-CDS at an index visit will be more likely to have naloxone rescue kits ordered in the intervention clinics than in the UC clinics within 30 days post-index.

Aim 2. To assess the impact of OUD-CDS on important patient outcomes of initiation and maintenance of Medications for Opioid Use Disorder (MOUD) in patients identified as having OUD or being at high risk for OUD.

H2.1: Patients identified as having OUD or as being at high-risk for OUD by the OUD-CDS at an index visit will be more likely to have MOUD orders or referral for OUD treatment within 30 days post-index in intervention clinics than in UC clinics.

H2.2: Patients identified as having OUD or as being at high-risk for OUD by the OUD-CDS at an index visit will have significantly more days covered by a MOUD prescription at 90 days post-index in intervention clinics than in UC clinics.

Aim 3. To assess the long-term impact of OUD CDS on important patient outcomes in patients with OUD or identified as high risk for OUD.

H3.1: Patients with OUD or identified as high-risk for OUD by the OUD-CDS who are cared for in intervention clinics will have significantly fewer post-index ED visits during the observation period (i.e., the period between each patient's index date and last observation) compared to patients cared for in UC clinics.

H3.2: Patients with OUD or identified as high-risk for OUD by the OUD-CDS who are cared for in intervention clinics will have significantly fewer post-index hospitalizations during the observation period compared to patients cared for in UC clinics.

Aim 4. To describe and quantify costs of OUD-CDS implementation and maintenance and the short-term cost impacts of the OUD-CDS.

H4.1: After controlling for demographics, baseline clinical status and prior costs of care, patients with OUD or identified as high risk for OUD by the OUD-CDS will have lower healthcare costs in intervention compared to UC clinics during the observation period (i.e., savings from lower ED visits and hospitalizations will outweigh increased costs of OUD treatment and naloxone rescue kits and OUD-CDS implementation and maintenance).

Aim 5. To use mixed quantitative and qualitative methods to identify, describe and quantify barriers and facilitators to implementation of the OUD-CDS so that it can be adapted to maximize its use and effectiveness.

5.2 Secondary Objective(s)

Among patients with OUD or identified as high-risk for OUD, we will assess secondary outcomes, which include whether those who are cared for in intervention clinics have lower rates of all-cause death and of fatal and non-fatal opioid overdoses during the intervention period compared to similar patients in UC clinics during the observation period.

Treatment effectiveness may vary as a function of contextual as well as patient factors. In secondary analyses, care system indicators (Site 1, Site 2, Site 3) and clinic characteristics (e.g., proportion of primary care patients eligible for OUD-CDS, proportion of clinic patients with government-sponsored insurance) may be added to the primary model as main effects and in interaction with the treatment group indicator to assess treatment heterogeneity due to contextual factors. Patient characteristics (e.g., race, ethnicity, age, estimated neighborhood income and education, documented heroin vs. oral opioid use) may be similarly added to the primary model to assess treatment heterogeneity due to patient factors.

The OUD-CDS tool is hypothesized to improve process measures of appropriate care for patients at high risk for or diagnosed with OUD by alerting PCPs to the risk of OUD and presenting them with tools and treatment advice that support the delivery of recommended care. For each PCP who practices at an intervention clinic, we will assess the extent to which engagement with the OUD-CDS (e.g., opening or printing OUD-CDS recommendations, use of embedded screening tools) is associated with patient outcomes. Via surveys, we will also assess PCP ratings of confidence in treating OUD and their satisfaction with the OUD-CDS.

5.3 Exploratory Objective(s)

In exploratory analyses, we may assess whether (a) PCPs in intervention clinics who are non-waivered at go-live dates are more likely to become buprenorphine-waivered than PCPs in UC clinics during the intervention period; (b) waivered PCPs in intervention clinics are more likely to prescribe buprenorphine than PCPs in UC clinics during the intervention period; (c) whether PCPs in intervention clinics who are non-waivered at go-live dates are reportedly more likely to prescribe buprenorphine should a waiver no longer be required than PCPs in UC clinics measured prior to go-live dates and at 9 months following go-live dates; (d) if we have adequate data, potentially via health plan or Surescripts data, whether adherence/persistence to methadone, buprenorphine, XR-NTX or therapy for patients with OUD differs for patients in intervention vs. UC clinics during the observation period; and (e) PCPs in intervention clinics are more likely to screen their patients for mental health conditions and infectious diseases than PCPs in UC clinics during the intervention period.

6.0 STUDY DESIGN

6.1 Overview of Study Design

We propose to implement OUD-CDS in a large multi-site clinic randomized pragmatic trial to evaluate its impact on practice process measures and patient outcomes. We also aim to prepare for scalability by evaluating facilitators and barriers to implementation, determining the costs of implementation and maintenance, and assessing cost effectiveness of the OUD-CDS. The trial will include three large geographically dispersed care systems that constitute a racially, ethnically and socioeconomically diverse patient population. At least 30 clinics will be randomized to receive the OUD-CDS intervention or UC. Randomization will be stratified by care system, with key pre-randomization clinic measures balanced across treatment arms. Randomization in each healthcare system will be approximately 1:1. In intervention clinics, the OUD-CDS will identify patients who are at high risk for or previously diagnosed with OUD; use data stored in the EHR for these patients to assemble treatment recommendations tailored to the current needs of each patient; display these recommendations via the OUD-CDS user interface; and store analytic data from all targeted visits. In UC clinics, the OUD-CDS will run invisibly in the background to identify high-risk and OUD diagnosed patients, assemble treatment recommendations and store analytic data from all targeted visits. The targeted visits for each study-eligible patient in all randomized clinics will be the index visit, the first visit at which the OUD-CDS identifies that the patient is eligible, and all post-index visits through the end of the observation period. Patients who are identified as eligible during the accrual period and meet all inclusion and exclusion criteria will be considered for inclusion in the primary outcome analyses. Patient outcomes will be derived from the data elements stored by the OUD-CDS at all targeted visits. To the extent it is available, EHR data from the year prior to the index visit through the end of the observation period will be included in primary and secondary analyses. Process outcomes at or following the index visit (Aims 1 and 2), and clinical outcomes following the index visit through the end of the observation period (Aim 3), will be compared between patients cared for in intervention and UC clinics to assess the effectiveness of OUD-CDS.

6.2 Duration of Study and Visit Schedule

Primary care clinics will be randomized within each health care system to receive or not receive access to the OUD-CDS. Once OUD-CDS is implemented in each health care system, its algorithms automatically identify eligible patients in all randomized intervention and UC clinics, independent of any PCP actions. PCPs in clinics with CDS access are anticipated to have access to the OUD-CDS intervention through May 2024, depending on factors such as healthcare system leader preference. In UC clinics, the OUD-CDS will run silently in the background over the same time period, collecting data without displaying. There is no study-determined visit schedule; rather, patient visits will be jointly determined by the patient and PCP. We plan to stop collecting outcome data in October 2023 at all sites. We anticipate patient observation periods of 19 to 31 months from date of index visit, depending on the site. Having the OUD-CDS run from implementation through the end of the observation period in all randomized clinics in each health care system ensures that identical methods are used to identify study-eligible patients and track patterns of OUD-related care so that we may quantify the impact of the OUD-CDS on OUD identification and care.

7.0 OUTCOME MEASURES

7.1 Outcome Measures

Primary outcome measures will include:

1. OUD diagnosis (in the problem list or as an ICD-10 visit code) within 30 days of index visit for patients identified by the OUD-CDS as being at high risk of OUD
2. Naloxone prescription within 30 days of index visit for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
3. MOUD orders or referral to OUD treatment within 30 days of index visit for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
4. Total days covered by an MOUD prescription in the 90 days after index visit for patients with OUD or identified by the OUD-CDS as being at high risk for OUD

Secondary outcome measures will include:

1. OUD diagnosis (in the problem list or as an ICD-10 visit code) at index or within 90 days of index visit for patients identified by the OUD-CDS as being at high risk of OUD
2. Naloxone prescription at index or within 90 days of index visit for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
3. MOUD orders or referral to OUD treatment at index or within 90 days of index visit for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
4. Number of ED visits during the observation period for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
5. Number of hospitalizations during the observation period for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
6. Healthcare costs during the observation period for patients with OUD or identified by the OUD-CDS as being at high risk for OUD, compared with healthcare costs over the same interval preceding the observation period
7. Cost of OUD-CDS implementation and maintenance
8. All-cause mortality rates during the observation period for patients at high risk of OUD
9. Fatal and non-fatal opioid overdoses during the observation period for patients at high risk of OUD
10. Rates of OUD-CDS use in intervention clinics
11. PCP ratings of confidence in treating patients with OUD prior to go-live date and 9 months following go-live date
12. Intervention clinic PCP ratings of satisfaction and acceptability of the OUD-CDS at 9 months following go-live date

Exploratory outcome measures may include:

1. Number of non-waivered PCPs becoming buprenorphine waivered during the intervention period, assessed via health system administrative data
2. Number of buprenorphine prescriptions written by waivered PCPs during the intervention period

3. PCP ratings of likelihood to prescribe buprenorphine for patients with OUD should no waiver be required, measured prior to go-live dates and at 9-months following go-live dates
4. Adherence to therapy during the observation period, assessed via Clarity and claims data
5. Number of patients diagnosed with OUD screened for mental health comorbidities and infectious diseases during the observation period

7.2 Study Timeline

After receiving Center for the Clinical Trials Network (CCTN) approval of the final protocol, approximately 9-12 months of trial preparation activities will elapse prior to commencing enrollment ("go-live") at Site 1. The intervention at Site 2 is anticipated to begin 6-9 months after go-live date at Site 1, and the intervention at Site 3 will begin 12-15 months after the go-live date at Site 1. Selection of Geisinger as Site 2 and Essentia as Site 3 occurred subsequent to the initial CCTN approval of the final protocol and initial IRB submission. Trial preparation will include obtaining Institutional Review Board (IRB) approval, customizing the OUD-CDS for each healthcare system, harmonizing data elements for EHR installation at each site, installing of EHR custom code at each site, recruiting and randomizing primary care clinics at each site, conducting PCP training at each site, integration of CDS into workflow at each site, and completing baseline PCP surveys at each site.

As noted previously, the COVID-19 pandemic delayed implementation by approximately 8 months. Accrual periods will range from 7 to 18 months based on site. During the accrual period, the study team will monitor accrual rates to determine when a sufficient number of patients have been enrolled to support the analysis plan. If enrollment is lower than expected, we may choose to extend the accrual period up to 3 additional months (through January 2023). Observation will begin with index dates at each site and are anticipated to continue through October 2023.

Anticipated Accrual + Observation Periods per Site:

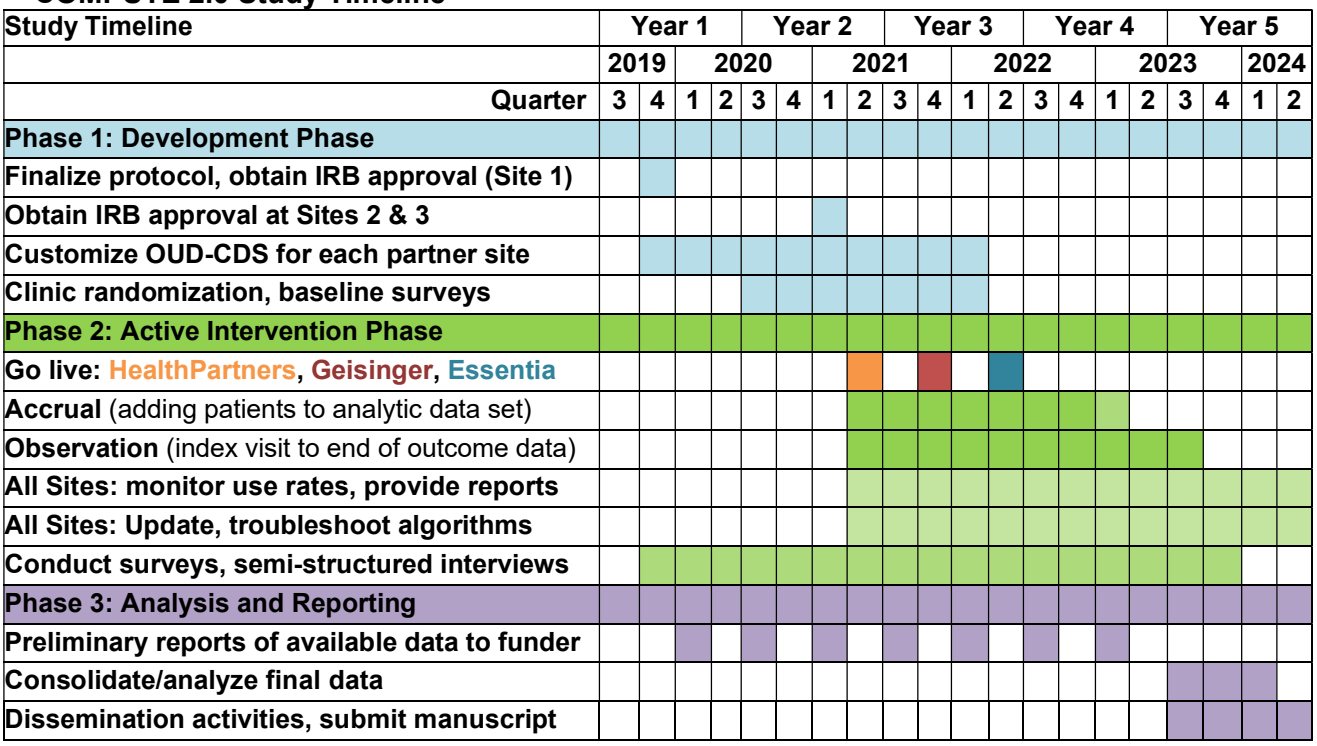
- HealthPartners – April 2021 to Oct 2023 (31 months)
- Geisinger – Dec 2021 to Oct 2023 (22 months)
- Essentia – April 2022 to Oct 2023 (18 months)

Anticipated Accrual* Periods per Site:

- HealthPartners – April 2021 to Oct 2022 (18 months)
- Geisinger – Dec 2021 to Oct 2022 (10 months)
- Essentia – April 2022 to Oct 2022 (7 months)

* We may extend the accrual period an additional 3 months based on enrollment trends.

COMPUTE 2.0 Study Timeline



8.0 STUDY POPULATION

8.1 Primary Care Clinics

This randomized clinical trial is a clinic-randomized study. A minimum of ten primary care clinics to be included in the study at each of three sites will be selected in partnership with primary care leadership at each site. To be eligible for randomization in this study, a primary care clinic must: (a) be included in one of the three care delivery systems included in this study, (b) have a minimum of 3 full-time PCPs who do not regularly work at any other primary care clinic, and (c) have an estimated minimum of 50 adult patients who meet study criteria for OUD or high risk for OUD. Exclusion criteria for potentially eligible primary care clinics include (a) plans to close or transfer ownership of the clinic within 24 months after the anticipated OUD-CDS go-live date, or (b) clinic not using their current EHR system for at least 12 months before the anticipated OUD-CDS go-live date at the clinic. Primary care clinics that have fewer than 50 patients at risk for OUD may not be eligible for randomization. However, consideration will be given to small clinics that may be part of a larger spoke and hub primary care clinic system, depending on the organizational structure of included care systems. For example, clinics X and Y in healthcare system 2 may be too small to consider randomizing them on their own, but because they are affiliated with clinic Z and most PCPs at clinic Z practice a day or two a week at clinics X and Y, clinics X, Y and Z would be randomized as one potential unit (thereby avoiding potential contamination).

Primary care clinics that pass all these eligibility and exclusion criteria will be randomized (within study site) using a validated computer-generated randomization scheme that takes into consideration such factors as overall clinic size, number of PCPs, number of buprenorphine PCPs, and baseline prevalence of diagnosed OUD. All PCPs and their study-eligible patients will be assigned to the treatment group of their randomized primary care clinic.

8.2 PCPs and Clinic Staff

To be eligible for inclusion in this study, a PCP must be a family physician, general internist, or adult-care non-obstetric nurse practitioner (NP) or physician assistant (PA) working at a study-eligible primary care clinic. PCPs who are and who are not buprenorphine-waivered are study eligible. PCPs in the intervention clinics will be encouraged but not required to use the OUD-CDS with eligible patients, so that the decision to use or not use OUD-CDS at a given clinical encounter is up the PCP at each clinical encounter. All PCPs will be asked to consent to and complete pre- and post-implementation surveys and may receive modest compensation for completing these surveys. In the intervention phase, PCPs who are high-, moderate- and low/non-users of the OUD-CDS will be invited to participate in interviews. Clinic staff associated with invited PCPs (e.g., rooming staff, nurses) will also be invited to participate. PCPs and staff who are asked to participate in interviews will be consented for those interviews and may receive modest compensation. Exclusive of consenting PCPs for interviews and surveys, we will request a waiver of written informed consent for PCPs from the IRB for the intervention because (a) the OUD-CDS is based on current national standards of OUD identification and management and does not make any treatment recommendations that are not accepted as community standard of care, and (b) consenting PCPs would compromise the external validity of the study by introducing selection effects. Measures to protect the privacy of PCPs participating in this study are described further

below. The OUD-CDS may also be turned on for non-PCP clinicians affiliated with intervention clinics, such as pharmacy staff, and a similar waiver of written informed consent will be requested by the IRB. These non-PCP clinicians may also be invited to participate in surveys or interviews.

8.3 Patients

To be eligible for inclusion in the study, a patient must meet all the following eligibility criteria: (a) be aged 18-75 years, inclusive, at the time of an index visit; (b) have been diagnosed with OUD, currently prescribed MOUD, or identified by study algorithms as being at high risk of OUD. There are no exclusions for pregnancy, lactation, or mental health or behavioral health issues. However, patients who meet the following criteria at the time of their index visit will be excluded and not be exposed to the OUD-CDS intervention: (a) those receiving active parenteral chemotherapy within the last year, (b) those with stage 4 or equivalent cancer diagnosis, (c) those enrolled in hospice care or palliative care programs. All women and members of racial or ethnic minority groups and their subpopulations who meet the above eligibility criteria and do not meet exclusion criteria will be included in accordance with the National Institutes of Health (NIH) Policy on Inclusion of Women and Minorities as Participants in Research Involving Human Subjects. A sample of patients with diagnoses of OUD and/or identified as being at high risk for OUD and/or referred by a PCP will be invited to participate in interviews and surveys. Patients who are asked to complete surveys or participate in interviews will be consented and will receive modest compensation. Beyond survey and interview participation, we will request and anticipate receiving a waiver of written informed consent from the governing IRB for patient participation because the study is minimal or less than minimal risk compared to the risk associated with any primary care encounter, and because the study could not be conducted if written informed consent were required to be obtained in the context of busy community-based primary care clinic environments. We have requested and received such waivers of written informed consent for patients in several similar prior studies. Note that patients who have requested non-participation in research studies at any of the participating care delivery systems will be excluded from all analyses.

Definition of High Risk: Algorithms determine when a patient is identified as being at high risk for OUD or opioid overdose, and, in intervention clinics, this will trigger a best practice alert to be displayed for a particular patient at a particular clinic encounter. These algorithms, like all of the OUD-CDS algorithms, are housed on a web platform that interacts with the EHR to pull data elements to run risk equations and determine patient eligibility. We anticipate that how the algorithms will identify patients at high risk of OUD or opioid overdose will evolve over time as our ability to predict risk improves. In early phases of this study, we may use EHR data elements such as long-acting opioid prescriptions, concomitant benzodiazepine and opioid prescriptions, mental health diagnoses, alcohol and substance use diagnoses and previous opioid overdose diagnoses to identify patients at increased risk of OUD or opioid overdose.[31] We may also use, in care systems where this is available, a risk equation developed and validated by EPIC that estimates a patient's risk of OUD or opioid overdose within the next year. As the study progresses, we anticipate incorporating additional calculators for high risk into our algorithms. In work funded by NIDA (1R01DA047724-01, PI Yarborough), we are developing risk calculators for suicide in people with OUD, as well as risk calculators for unintentional opioid overdoses, in a population of nearly 8 million patients across 7 care systems. Variables in these risk models will include prescription opioid use, prescription opioid use reduction, prescription opioid discontinuation, opioid-related overdose, OUD and/or MOUD prescription, and illicit opioid use.

As more sophisticated risk equations for OUD and opioid overdose risk become available, our team will write new draft algorithms to identify patients at risk in Visio. Once we have a good understanding of how these draft algorithms would work with the data available to us in EPIC, we will meet with the DSMB to discuss this potential change in identification of at-risk patients to present our proposed changes, receive feedback, make any necessary edits and request approval. Once approved, these risk equations would replace the previous risk equations in our algorithms at a pre-specified and documented date and time, and would be used to identify patients at risk of OUD or opioid overdose. Any and all changes in these OUD-CDS algorithms will be documented in a log to allow us to take these changes into account in analyses and understand how such changes may have influenced study outcomes. For each patient at each encounter, we will know why that patient was identified as high risk.

8.4 Healthcare System Leaders

We will work with study teams and healthcare system leadership at each site to identify up to 15 leaders at each site with various levels of engagement with the OUD-CDS implementation and oversight to provide input into perceived value of the OUD-CDS, barriers and facilitators to implementation of the OUD-CDS, and costs associated with implementation and maintenance. Leaders will be recruited to provide wide representation of influence within the organization, including high-level decision makers and mid-level supervisors, such as clinic manager and care team leaders. Leaders will be consented to participate in interviews.

8.5 Strategies for Recruitment and Retention

Clinic Recruitment and Retention: Our team will work as directed by the funding agency, their contractors, and the study teams and clinical leadership at each healthcare site to determine which primary care clinics will be eligible for inclusion in this study. All PCPs and their patients who meet the criteria defined in **Sections 8.2 and 8.3** will be included in this study.

Through prior work, we know that feedback about use rates of the OUD-CDS tool, provided at the clinic level and the individual PCP level, is crucial for achieving and maintaining high use rates of the CDS tool, essentially one important measure of retention and continued engagement. To promote high and sustained use rates of the OUD-CDS, we will work with each system's primary care leadership to identify to which clinic leaders such use reports should be sent, and whether we will be able to offer incentives to clinics to achieve and maintain high use rates. In previous studies, incentives have included clinic lunches or contributions to the general clinic fund that is used to pay for such things as flowers to mark important life events for clinic employees.

Strategies to achieve and maintain high use rates may include the following multi-pronged strategies:

1. We will use a multi-level approach to prompt PCPs to screen and treat patients for OUD. Depending on the healthcare system, this will include several or all of the strategies below, and potentially additional strategies based on healthcare system leader recommendations. After a high-risk patient is screened and not assessed to have OUD, all alerts for that patient would be silenced for a period of time depending on the underlying algorithms.

a. We will display a best practice advisory (BPA) for rooming staff in EPIC that prompts the rooming staff to print the patient and PCP interfaces of the tool with one click. The patient printout prompts patients to discuss any concerns they have about opioid use with their PCP, while it notifies the PCP that this is a patient who has been identified as needing screening and possibly treatment for OUD. It will also alert patients and PCPs when OUD has been identified in the electronic health record, with or without corresponding MOUDs.
b. We will prompt the screening of patients identified at high risk for OUD at refill encounters for opioid medications. Such encounters may occur either in clinic with the PCP, via phone with registered nurse (RN) refill encounters, or via other encounter types depending on the care system.
c. At healthcare systems that require that PCPs complete contracts with their patients that outline agreements re: use of their opioids, we will prompt assessment of patients for OUD when those contracts are due to be renewed. At HealthPartners, such contracts occur annually and are identified via a health maintenance alert in EPIC. Our team will work to determine whether such opioid contracts are employed at Sites 2 & 3, whether they are tracked/prompted in EPIC, and whether these encounters may provide additional opportunities for OUD screening.

2. We will provide monthly clinic- and provider-level feedback of use rates to clinic leadership, and, where allowed, offer clinic-level incentives to achieve and maintain high use rates. In other CDS studies, we have found that providing clinic-level and PCP-level use reports data has dramatically improved and sustained use rates for the duration of the intervention.

   One month after each healthcare system's go-live date, study staff will begin sending intervention clinic leaders monthly reports that include (1) each clinic's use rate of the OUD-CDS in the previous month, compared to other clinics in that healthcare system (and, as available as the study progresses, previous months' use rates), ranked from highest-use clinics to lowest-use clinics, and (2) the use rates for each primary care provider (PCP) in that particular clinic (i.e., clinic leaders only get use rate reports at the PCP level for their own clinic, not other primary care clinics). Accompanying these monthly use rate reports is clear communication of the use rate goal of 60% or more of targeted encounters, and, where allowed, the threshold to reach a clinic incentive (such as achieving target use rates for at least 3 consecutive months to earn a clinic lunch).

   The example report below is from an implementation of a cardiovascular decision support tool, where target use rates were 80% of eligible encounters. Leadership at every primary care clinic in that care system received emailed monthly reports.

Clinic	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan
Clinic A	93%	91%	95%	92%	92%	94%	93%	92%	76%	83%	86%	96%	96%
Clinic B	93%	90%	91%	91%	94%	93%	95%	95%	92%	96%	96%	81%	95%
Clinic C	98%	97%	98%	97%	95%	94%	91%	85%	93%	83%	95%	98%	94%
Clinic D	89%	98%	96%	98%	99%	93%	83%	74%	78%	86%	91%	97%	92%
Clinic E	99%	93%	90%	95%	95%	95%	87%	88%	95%	93%	91%	92%	91%
Clinic F	94%	98%	94%	91%	86%	89%	95%	94%	97%	76%	65%	75%	90%
Clinic G	95%	92%	88%	92%	94%	94%	98%	95%	95%	95%	91%	84%	88%
Clinic H	96%	93%	95%	96%	92%	93%	96%	91%	83%	89%	75%	80%	87%
Clinic I	78%	94%	94%	86%	89%	68%	65%	49%	49%	74%	93%	88%	77%
Clinic J	71%	78%	91%	86%	92%	69%	84%	88%	57%	64%	83%	73%	75%
Clinic K	81%	68%	78%	85%	95%	91%	83%	70%	88%	88%	79%	79%	69%
Clinic L	90%	90%	91%	90%	88%	93%	87%	76%	65%	72%	66%	51%	64%
Clinic M	77%	76%	64%	70%	52%	63%	74%	78%	81%	82%	78%	83%	81%
Clinic N	55%	63%	79%	73%	71%	57%	63%	74%	74%	73%	82%	79%	74%

Key:
Green= Use rates at or above 80% goal
Yellow = Use rates below goal (65%-79%)
Red = Use rates significantly below goal (<65%)

At the clinic level, clinic leaders will also be provided with a monthly use rate report by PCP:

Clinic H Wizard Use Rate Report: December 2018	# Eligible Visits	% Visits where CV Wizard Opened and Printed
CLINICIAN A	56	100%
CLINICIAN B	11	100%
CLINICIAN C	112	100%
CLINICIAN D	95	88%
CLINICIAN E	39	62%
CLINICIAN F	81	61%
CLINICIAN G	58	43%
CLINICIAN H	0	N/A
TOTAL	452	85%

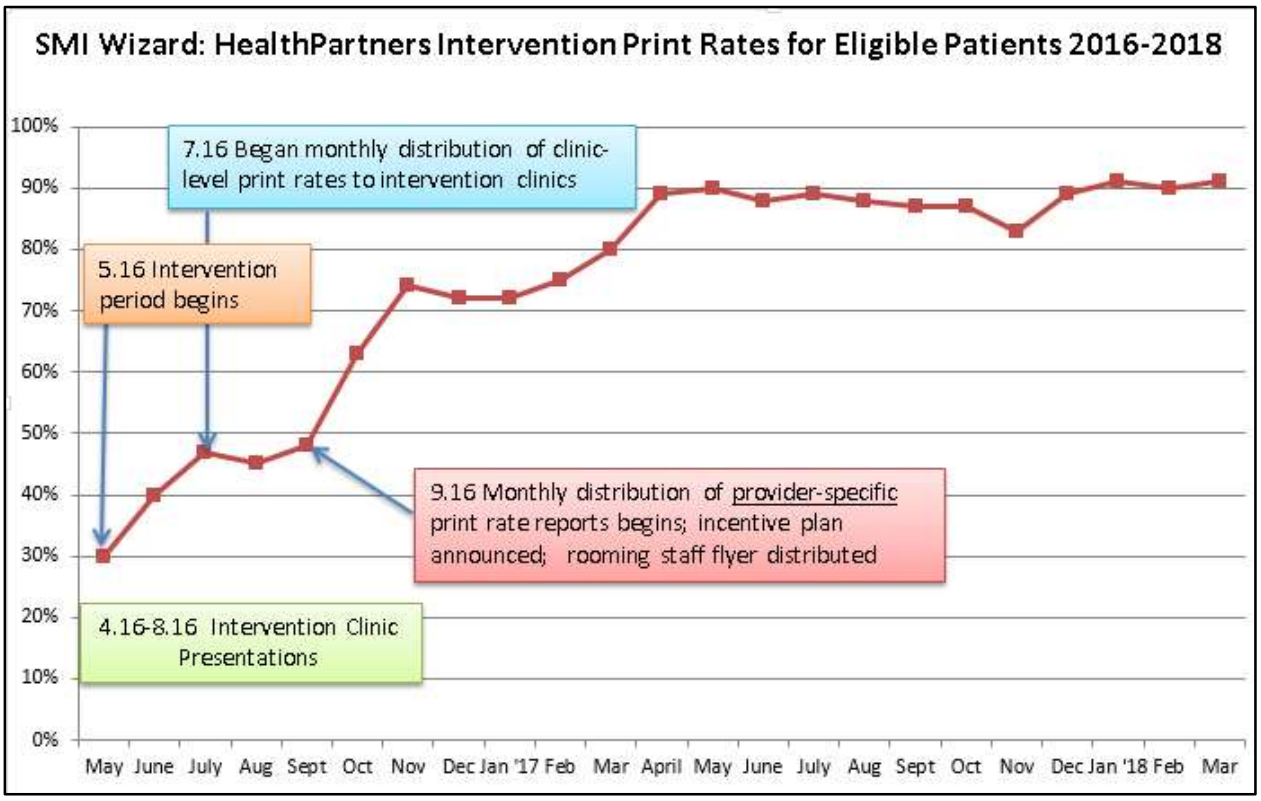
Clinics will have two months following the go-live date to bring their use rates up to the 60% of eligible encounters target use rate. After that run-in period, study staff will reach out to clinic leaders by email and/or by phone to discuss use rates that are below targeted rates. Study staff will review both the clinic-level and PCP-level reports with clinic leaders

and discuss potential strategies for increasing use rates, including training or retraining for rooming staff of PCPs with low use rates and qualitative interviews with care teams to understand potential barriers to use (Is the rooming staff seeing the best practice alert? Are there issues with being able to print the CDS? Does the PCP feel he or she doesn't have time to integrate this tool with their usual workflow, or that OUD is not a clinical priority for his or her patients?) and any concerns or questions about the OUD-CDS tool itself.

3. We will conduct a pre-implementation pilot phase at each site that includes qualitative data collection from PCPs and patients experiencing the OUD-CDS and make any improvements needed to the tool and workflow prior to live implementation. The step-wise evaluation of the OUD-CDS by site roll-out will inform the implementation at subsequent sites. Ongoing evaluation during implementation will offer continuous process improvement for the OUD-CDS with a goal of optimizing PCP use rates.

4. One example of the effectiveness of these strategies is seen in Serious Mental Illness Wizard (SMI), an NIH-funded study that aimed to reduce cardiovascular risk in people with SMI. Our team used clinic-and PCP-specific use rates and clinic lunch incentives to achieve use rates well above the goal of 80% of eligible encounters. Of note, the best practice alert was sent to rooming staff, not the PCP, accounting for the higher baseline rates (prior to use rate report feedback) of 30% vs 5% in the COMPUTE pilot study.

Figure 4. Print Rates over the Intervention Period for SMI Wizard



Patient Recruitment: A random sample of patients eligible for recruitment for surveys and interviews will be identified. Patients will be recruited via mailed letters or e-mail. Surveys will be completed online via a link or QR code provided in the letters or emails, and consent to participate

will be included in the online survey. Interviews will be completed via phone or in person, according to patient preference. Consent will be obtained verbally after the patient reviews the elements of consent included in the recruitment letter and also asks any questions of the interviewer. Modest compensation will be provided for patient surveys and interviews.

PCP and Clinic Staff Recruitment: All randomized PCPs will be invited to participate in surveys via email prior to the go-live date and during early implementation (9-months after go-live date). Consent to participate in the survey will be included in the online survey. A sample of PCPs eligible for recruitment for interviews will be identified from administrative data, and PCPs and their clinic staff will be invited to participate via email. Interviews will be completed via phone or in person, according to PCP/staff preference, and consent will be obtained verbally after the interviewee reviews the elements of consent included in the recruitment letter and asks any questions of the interviewer. Modest compensation may be offered for PCP surveys and PCP or clinic staff interviews.

Leader Recruitment: Clinic and administrative leaders will be identified for interviews in partnership with healthcare leadership and site investigators, and leaders will be invited to participate via email. Interviews will be completed via phone or in person, according to leader preference, and verbal consent will be obtained.

9.0 SITE SELECTION

9.1 Number of Sites

Healthcare Systems

HealthPartners, Geisinger and Essentia will participate in this study.

Primary Care Clinics

At least 30 primary care clinics from three healthcare systems will participate in this study.

9.2 Site Characteristics

Healthcare Systems

Requirements for the Two Additional Healthcare Systems (assessed via surveys distributed on 4/17/19. Several items were optional and are so indicated. Six healthcare systems returned surveys to express interest in participating in COMPUTE 2.0, and all six satisfied required criteria).

1. Use of EPIC 2018 or later
2. Willingness to use active guidelines (an existing module within EPIC)
3. Willingness to accept custom code
4. Use of EPIC Interconnect with clinical services turned on
5. Willingness to add an alert to initiate activity around opioids to EPIC, such as a generic navigator report section or a BPA
6. Willingness to run Opioid Wizard during primary care office visits
7. Willingness to allow custom doc flowsheet rows and smart data elements to file back into EPIC
8. Willingness to allow the prime site to remotely view and help troubleshoot issues in the EPIC Development environments with the site's EPIC team
9. Use of the EPIC Beaker lab module (optional; informative question only)
10. Access to EPIC via Citrix (optional; informative question only)
11. Access to EPIC via VDI (optional; informative question only)
12. Ability to provide preliminary data to assess feasibility of the site, such as number of patients per clinic, general demographics, opioid prescriptions, OUD diagnoses, or prevalence of patients using medications for OUD (i.e., buprenorphine, XR-NTX, and methadone)
13. At least 10 primary care clinics that operate under one EPIC instance with centralized Information Technology (IT) that are willing to participate and be randomly assigned to a treatment group by clinic
14. Care system willingness and ability to encourage PCPs to become waivered to prescribe buprenorphine.
15. Leadership support for managing OUD patients in primary care when appropriate
16. The availability of a site Principal Investigator (PI), clinical champion, project manager, EPIC analyst and data programmer. If there is not an EPIC analyst available, access to an EPIC team that can help implement the OUD-CDS in a timely manner

17. The availability of researchers who are highly engaged with the care system who can assess the healthcare system's willingness to implement the OUD-CDS within EPIC
18. The ability to procure a letter from the IT group and care system leadership indicating support of implementation of the OUD-CDS
19. The ability to obtain timely IT security clearance
20. The ability of the organization to sign a business associate's agreement or service agreement for OUD-CDS services
21. The ability to harvest data from Clarity
22. The willingness to allow the prime site to retain a limited data set for analysis (provided that the appropriate agreements are in place and the IRB allows this, depending on requiring or waiving consent)
23. Willingness to cede to a central IRB
24. Access to claims data (Medicare, commercial or Medicaid; optional)
25. Use of the EPIC 2018 adherence module or access to Surescripts pharmacy dispense data (optional)

9.3 Rationale for Site Selection

A total of three study sites involving at least 30 primary care clinics (at least 10 primary care clinics in each healthcare system) will provide for diversity in primary care practices, patient race and ethnicity, geographical distribution, and rural/urban representation.

HealthPartners will serve as Site 1 for this study and served as the sole site for the CTN-0076-Ot pilot study. HealthPartners is the largest consumer-governed nonprofit health care organization in the country, providing care, coverage, research, and education to improve health and well-being in partnership with its members, patients and community. HealthPartners serves more than 1.5 million medical and dental health plan members and more than1 million patients in its HealthPartners Medical Group (HPMG) and Park Nicollet Medical Group (PNMG) clinics and hospitals. In 2013, HealthPartners and Park Nicollet combined under the name HealthPartners and a single consumer-governed board of directors. The new organization includes a multispecialty group practice of more than 1,700 physicians, seven hospitals, 47 primary care clinics, 22 urgent care locations, 22 dental clinics, and numerous specialty practices in Minnesota and western Wisconsin. The majority of HPMG and PNMG patients (>80%) have commercial health insurance, while approximately 6% are insured via Medicare and 4% via Medicaid. HPMG and PNMG offer outpatient primary and specialty addiction care, day programs, partial hospitalization programs and inpatient treatment for OUD and other substance use disorders. The medical groups refer out for methadone maintenance; for the approximately 40% of patients who are also HealthPartners Insurance members, we will be able to capture data on their methadone prescription dispensings.

The remaining two study sites, Geisinger and Essentia, were selected based on the availability and engagement of an effective clinicians champion, and the care system's ability to: (a) obtain adequate support from their primary care and other care system leadership, (b) modify and install custom EHR code, (c) help determine best ways to integrate the CDS into their clinical workflows and achieve and maintain high clinical use, (d) provide required training for PCPs and staff, and (e) obtain timely IT security clearance and a letter of support from their IT group. These criteria are imperative for ensuring proper functioning and maintenance of the OUD-CDS. They were also

selected based on their ability to provide diversity in primary care practices, patient race and ethnicity, geographic distribution, and rural/urban representation.

Primary Care Clinics

In this clinic-randomized trial, decisions about which primary care clinics may be ineligible for inclusion will be made in partnership with primary care leadership. Primary care clinics that have fewer than 50 patients meeting eligibility criteria may not be eligible for randomization. However, consideration will be given to small clinics that may be part of a larger spoke and hub primary care clinic system, depending on the organizational structure of included care systems. For example, clinics X and Y in healthcare system 2 may be too small to consider randomizing them on their own, but because they are affiliated with clinic Z and most PCPs at clinic Z practice a day or two a week at clinics X and Y, clinics X, Y and Z would be randomized as one potential unit (thereby avoiding potential contamination).

10.0 STUDY PROCEDURES

10.1 Index Visit

There is no study-determined visit schedule. Patient visits with their PCPs in the randomized clinics will take place without any interference or involvement from the study team. The first visit at which the OUD-CDS algorithms determine that a patient is eligible for the intervention will be denoted as the index visit.

10.2 Randomization

The OUD-CDS software is a system level intervention comprised of 1) a passively operating web service that gathers, analyzes and retains information pertinent to every web service call, and 2) a user interface that presents a summary of algorithm results to front end users. The web service documents every web service call made by all front-end users in all participating locations so that data pertinent to all targeted visits from all eligible and enrolled patients will be identically collected and available in both treatment arms. The user interface will function as the intervention delivery vehicle and therefore be operative only in intervention locations. Intervention or Control designation will vary randomly by clinic. The OUD-CDS web service will therefore operate passively in all participating clinics but the user interface will only be turned on in clinics that are randomly assigned to the intervention treatment group.

To the extent that patients tend to receive most of their care over time at a single clinic, and that clinicians tend to practice at a single clinic, it is reasonable to assert that the risk of intervention contamination across clinics is low. However, because it is common for patients to see more than one clinician in a clinic location over time, and for clinicians within a clinic location to discuss aspects of care delivery with each other, the risk of intervention contamination within clinics is rather high. Randomizing by clinic rather than by PCP or patient will minimize risk of intervention contamination.

Generally speaking, randomization should balance treatment groups on factors that enhance or impede intervention uptake and adherence, that are related to and including study outcomes, and on any other unmeasured factors that may affect statistical power. However, the likelihood that factors related to these considerations are balanced may be diminished in cluster-randomized trials due to relatively few randomized units.[33, 34] Covariate constrained randomization of the clinics will be implemented to balance treatment groups across the study and within health care systems (strata) on factors related to study outcomes, implementation of the intervention, and potential treatment modifiers. Potential balancing factors include:

- % of all patients with diagnosed OUD with a current MOUD
- % of all patients with diagnosed OUD
- % of all patients at high risk for OUD
- % of patients at high risk for OUD provided a with naloxone rescue kit
- n of adult patients at clinic
- % of adult patients with government sponsored insurance
- % of adult patients who are non-Hispanic White
- n of waivered providers

Each patient will be considered to belong to the clinic in which his or her first visit that is eligible for the OUD-CDS intervention (i.e., index visit) takes place, and as such will be in the treatment group to which their clinic was randomly assigned. Post-index visits may take place in the same or different clinics or treatment groups relative to the index visit and may or may not be eligible for the OUD-CDS to offer treatment recommendations. In keeping with an intent-to-treat principle, all index and post-index visits and outcome measures for each patient will be attributed to the treatment group assignment of the clinic where the index visit took place.

10.3 Treatment/Intervention

The intervention is the availability of the OUD-CDS display in approximately half of randomized primary care clinics.

10.4 Premature Withdrawal of Participants

Once randomized, all primary care clinics are anticipated to remain enrolled for the duration of the study. All PCPs in randomized clinics will be followed for the duration of the study unless they die or leave the employment of the clinic. All study-eligible patients with OUD or identified by the algorithms as being at high risk of OUD in randomized clinics will be followed for the duration of the study unless they die or leave the care system. Patients who have opted out of research will be excluded from all analyses.

10.5 Study Halting Rules

Reasons for the DSMB, investigator or sponsor to halt the study may include, but are not limited to, lack of funding or early termination of the study for safety reasons. If the study is prematurely terminated or temporarily suspended, the PI will promptly inform the IRB and sponsor and provide the reason(s) for the termination or temporary suspension.

10.6 Follow-Up

There is no study-determined visit schedule. Patient visits with their PCPs in the randomized clinics will take place without any interference or involvement from the study team. Primary care visits that take place after the index visit and prior to the end of the observation period will be denoted as post-index visits. The OUD-CDS will flag the occurrence of all index and post-index visits so that EHR data documented from each may be extracted and assembled into an analytic dataset.

10.7 Participant Reimbursement

We will not be directly reimbursing PCPs and patients to participate in the OUD-CDS intervention. However, where allowed by participating healthcare system leadership and when approved by the IRB of record, we will be offering clinic incentives to encourage high use rates of the OUD-CDS (see **Section 8.5**). Additionally, we may offer incentives to PCPs to complete surveys and to PCPs and clinic staff to participate in interviews where allowed by participating healthcare system leadership and when approved by the IRB of record. This may include, but is not limited to, cash incentives, gift cards, donations to charities or chocolates. We will offer patients modest monetary incentives to participate in surveys and interviews. We do not plan to offer clinic or administrative leaders incentives to participate in interviews. At healthcare systems where this is allowed, we may provide incentives to PCPs in randomized clinics (i.e., PCPs in both intervention and UC clinics) to become buprenorphine-waivered during each site's implementation period.

11.0 STUDY ASSESSMENTS

11.1 Table of Assessments

Table 1. Assessment of Primary, Secondary and Exploratory Outcomes

Outcome	Timing*	Data Source
OUD diagnosis	Index date, 30 days, 90 days	EHR/OUD-CDS data
Naloxone prescription	Index date, 30 days, 90 days	EHR/OUD-CDS & Claims data
MOUD orders or referral	Index date, 30 days, 90 days	EHR/OUD-CDS & Claims data
days covered by MOUD prescription	Index date, 30 days, 90 days	EHR data
ED visits	Observation period	EHR & Claims data
Hospitalizations	Observation period	EHR & Claims data
Health care costs	Observation period, with pre-observation period matched for number of days	EHR & Claims data
Costs of OUD-CDS implementation and maintenance	Mid-intervention period	Interviews/surveys with implementation site staff
All-cause mortality	Observation period	EHR data, Claims data, State mortality data
Opioid overdoses	Observation period	EHR & Claims data
OUD-CDS use rates	Intervention period	EHR/OUD-CDS data
PCP confidence in treating patients with OUD	Baseline, 9 months	PCP surveys
PCP ratings of likelihood to prescribe buprenorphine for patients with OUD should no waiver be required	Baseline, 9 months	PCP surveys
Intervention PCP ratings of OUD-CDS satisfaction and acceptability	9 months	PCP surveys
Waivered PCPs	Pre-intervention, intervention period	Administrative data
Buprenorphine prescriptions written by waivered PCPs	Intervention period	EHR/OUD-CDS data
Adherence to therapy	Intervention period	EHR/OUD-CDS data
Screening for comorbid conditions	Observation period	EHR/OUD-CDS data

***Definitions:**
Index Date
- Varies by patient
- First visit at which the OUD-CDS identifies that the patient is study eligible

Intervention Period
- Varies by system
- OUD-CDS implementation date through a predetermined time at which the Wizard interfaces will be turned off in the intervention clinics

Observation Period
- Varies by patient
- Index visit date through a predetermined time at which no more outcome data will be included in the analytic sample

11.2 Mixed Methods

We will rely on the RE-AIM framework to construct a quantitative monitoring system that will identify implementation problems as early as possible, followed by selective interviews and surveys to identify specific barriers and facilitators that can be addressed iteratively as each site initiates the OUD-CDS. We will also document any adaptations made and their impact on our measures. The RE-AIM constructs and measures are listed in **Table 2**.

Table 2. RE-AIM Evaluation and Monitoring System

Constructs	Evaluation Goal	Quantitative Measures
Reach	Maximize the eligible patients receiving the OUD-CDS during primary care encounter	% of eligible encounters in intervention clinics for which the OUD-CDS is opened and used
Effectiveness	Maximize the effectiveness of the OUD-CDS tool to achieve study outcomes.	% of study eligible patients who receive an OUD diagnosis, naloxone, MOUD, referral for OUD treatment, or screening for infectious diseases or mental health conditions
Adoption	Minimize the variation in Reach, Effectiveness, and Implementation across different clinics and clinicians	Size of one standard deviation among clinics and among clinicians in the process and outcome measures listed under reach and effectiveness
Implementation	Maximize fidelity to optimal intervention with patients or modify the intervention to fit clinic realities	% of patients with an OUD diagnoses who refill MOUDs, attend therapy appointments or return for follow-up care
Maintenance	Maintain the optimal level of patient intervention over time	Change in RE-AIM measures over time

The following methods will be used to conduct an assessment of the reasons for problems identified by the monitoring system and identification of barriers and facilitators to the use of the OUD-CDS through a mixed-methods approach guided by the measures in the monitoring system

above. The monitoring data will be collected routinely at each clinic and site as it implements either pilots or full implementation. Findings from early monitoring will inform the need for interviews with key informants to identify changeable barriers and facilitators. Adaptations and adjustments to the intervention delivery and learnings from earlier sites will inform the implementation approach at subsequent clinics and sites. The data collection and analysis methodology for each data collection event is meant to be rapid in nature, so as to make the most expedient and beneficial use of the findings during active implementation. However, a larger implementation analysis will conclude in the later phase of the study in order to inform broader dissemination recommendations in other settings. In order to maximize the benefit of early learnings, qualitative investigators at subsequent sites will be involved in planning and analysis of both monitoring activities and qualitative data.

Pre-Implementation/Design Phase Activities

1. Design phase PCP interviews: Conduct up to 10 semi-structured interviews with key informants (PCPs, clinic staff and health system leaders) about the design and workflow for the OUD-CDS and related post-index follow-up care to ensure acceptability, and feasibility of the intervention design.
2. Design phase patient interviews: Conduct up to 30 semi-structured interviews at baseline with patients previously diagnosed with OUD, identified as high risk for OUD, or referred by their PCP about the design, content, and messaging of any patient-facing materials related to the OUD-CDS and patient perspective on discussing opioid related care in primary care encounters.
3. Plan data monitoring approach: Plan and construct a monitoring system to identify in real time the use of the OUD-CDS and intervention-related post-index care at the levels of the health system, randomized clinics, individual clinicians, and individual patients. This monitoring system will be utilized during active implementation to provide feedback to clinics and system leaders and support the ongoing assessment of barriers and facilitators to the use of the OUD-CDS as well as modifications in adoption and implementation.
4. Mini-pilot: Conduct a mini-pilot or other usability testing of the OUD-CDS with a small number of clinicians in order to test the OUD-CDS tool and the monitoring and feedback system. Collect feedback from pre-pilot clinicians and other clinic staff through site visits and refine the design and workflow.
5. Pilot: Pilot test the OUD-CDS in 1-2 clinic sites in the care system.
6. Finalize implementation plan: Make adjustments to final implementation analysis where feasible and necessary, and document implementation-related issues from multiple stakeholder perspectives prior to moving forward.
7. Baseline PCP surveys: Collect baseline surveys (prior to vanguard or overall go-live dates, depending on clinic) of all PCPs in randomized clinics to assess confidence in assessing, diagnosing, treating, and referring patients with OUD.

Implementation Activities

1. Monitoring: Produce monitoring data reports developed during the pre-implementation phase that describe the use of the OUD-CDS and the types of post-index follow-up care received by patients identified via OUD-CDS.
2. Feedback: Distribute monitoring reports to clinic leaders on a periodic basis (at least monthly).
3. Interview selection: Utilize the monitoring reports to identify and compare characteristics of clinics and clinicians with high and low rates of OUD-CDS use as well as high and low proportions of patients receiving post-index care.
4. PCP/staff/leader interviews: Conduct up to 30 semi-structured interviews with clinicians, clinic staff and health system leaders in OUD-CDS randomized clinics to identify the main barriers and facilitators to the use of OUD-CDS, solicit suggestions for improving the intervention and post-index follow-up care, and understand support for maintaining or modifying the OUD-CDS system after the research project.
5. Patient interviews: Conduct up to 90 semi-structured interviews with patients previously diagnosed with OUD, identified as high risk for OUD, or referred by their PCP to gather reactions and suggestions for improving the intervention from the patient perspective.
6. Patient Surveys (0-6 months after go-live date): Collect up to 130 patient surveys to test and quantify conclusions developed from the patient interviews.
7. Adaptation: Work with system and clinic leaders to devise and implement adaptations to the original design and workflows that address any barriers identified above and document all changes and known factors contributing to barriers and facilitators.
8. Adaptation: Make continuous recommendations to Sites 2 and 3 about their implementation plan based on findings from early implementation analysis in Site 1.
9. Follow-up PCP Surveys (9-months after go-live date): Collect 9-month surveys of all primary care clinicians in randomized clinics to assess change in confidence assessing, diagnosing, treating, and referring patients with OUD. Include set of questions about the usability, accuracy, likelihood to recommend the tool, and barriers and facilitators identified through the clinician interviews for PCPs in OUD-CDS randomized clinics.

The above series of activities will be repeated at each site. Data collected will be analyzed rapidly and any adjustments to the intervention needed to optimize the uptake of the intervention will be made and applied to subsequent sites.

Subject Recruitment and Data Collection

A. PCP Surveys

All PCPs in intervention and control randomized clinics will be surveyed at Baseline and 9 months to assess change over time in PCP's perceived ability to appropriately assess, diagnose, treat, and refer patients with OUD and their satisfaction with the OUDS-CDS. Baseline surveys will be conducted in the 1-2 months prior to intervention going live in each care system. A vanguard phase for each care system will occur approximately 2 months prior to each care system's official go-live date to pilot the roll-out of the baseline surveys and go-live procedures in a select subset of clinics. Follow-up surveys will be conducted after the intervention has been live for 9 months in each system.

For PCPs in intervention-randomized clinics, the 9-month surveys will also include a portion regarding barriers and facilitators to use of the OUD-CDS tool itself. Questions assessing the use of the tool in the 9-month survey will be designed by the study team based on findings during the early implementation phase from the quantitative monitoring data and qualitative interview data. This section of questions will help quantify barriers and facilitators to PCP use of the OUD-CDS.

Samples for PCP surveys will be identified by the on-site study teams for recruitment and data collection. Samples will include all clinicians working as PCPs in study-randomized clinics at the time of the survey.

The DSC will work with the Lead Node and each study site to construct a survey that will be acceptable within each care system. The survey data will be collected by the DSC electronically. The DSC will provide each study site with a list of unique survey links, one of which will be included in each invitation to a PCP to respond to the survey. The survey will appear to originate within the health system. All surveys will include a consent form which will allow the respondent to agree to the collection and storage of the respondent's data prior to proceeding with the survey. Clinicians may receive an incentive for participation.

The initial PCP survey ("Baseline Survey") will focus on confidence in their ability to appropriately assess, diagnose, treat and refer patients with OUD, assessed via 4- or 5-point Likert scales. At intervention end, PCPs will again be surveyed about their confidence in OUD care ("Follow-up Survey"), and PCPs in intervention clinics will also complete survey questions specific to the OUD-CDS, including questions regarding usability, accuracy, and provider likelihood to recommend the tool. A draft of specific items in the surveys follows. The survey draft that follows is provided as an example, is subject to change, and may differ slightly between healthcare systems.

Draft of Primary Care Provider Survey for COMPUTE 2.0
Please answer the following questions to the best of your ability. Your answers will help us understand the impact Opioid Wizard may have on clinician ability to diagnose and treat opioid use disorder, and the usefulness of the tool.

1. What is your primary clinic?

2. What is your age?

3. What is your gender

4. With which race/ethnicity do you identify?
- Asian
- Hispanic
- Native American/Alaskan Native
- Non-Hispanic black
- Pacific Islander/Native Hawaiian
- White
- Mixed race or other
- Prefer not to answer

5. How many years have you been in practice following residency or fellowship?
- 0-5
- 6-10
- 11-15
- 16-20
- 21+

6. What is your medical specialty?
- Family Practice
- Internal Medicine
- Med Peds
- Other (please specify)

7. On average, how many days a week do you see patients in clinic?
- 0
- 1
- 2
- 3
- 4
- 5 or more

Answer the questions below about your knowledge and approach to management of patients with Opioid Use Disorder (OUD). Choose only one answer.

8. How often do you formally assess patients for opioid use disorder (OUD)?

Very often | Often | Sometimes | Occasionally | Never

9. How confident do you feel about screening your patients for OUD?

Very confident | Moderately confident | Somewhat confident | Not at all confident

10. How often do you provide treatment or refer your patients for treatment of OUD?

Very often | Often | Sometimes | Occasionally | Never

11. How confident are you at diagnosing patients with OUD?

Very confident | Moderately confident | Somewhat confident | Not at all confident

12. How confident are you at treating your patients with medications such as buprenorphine or naltrexone for OUD?

Very confident | Moderately confident | Somewhat confident | Not at all confident

13. How confident are you that you know when to refer your patients with OUD for treatment by addiction specialists?

Very confident | Moderately confident | Somewhat confident | Not at all confident

14. (Skip if PCP waivered to prescribe buprenorphine) To what extent do you agree or disagree with the following statement: The availability of EHR-integrated clinical decision support for how to use buprenorphine and/or naloxone and manage OUD would make it more likely that I would become a certified buprenorphine prescriber.

Strongly agree | Somewhat Agree | Somewhat Disagree | Strongly disagree

15. Please rate your ability to effectively manage patients with the following treatment strategies:

	High ability (on par with subspecialists)	Moderately high ability	Adequate ability	Some ability; could use improvement	Low ability
Brief motivational counseling	1	2	3	4	5
Overdose prevention	1	2	3	4	5
Extended-release naltrexone (Vivitrol)	1	2	3	4	5
Buprenorphine (as monotherapy or in combination with naloxone (Suboxone))	1	2	3	4	5
Referral for methadone	1	2	3	4	5

NOTE: **The follow-up survey will repeat the questions above, and, for PCPs with CDS access, these additional questions will be asked**

Please answer the questions below concerning work flow and ease of use of the Opioid Wizard Clinical Decision Support.

16. How likely are you to recommend Opioid Wizard to a colleague?

Very likely | Moderately likely | Somewhat likely | Not very likely | Not at all likely

17. Opioid Wizard is a tool that helps me screen for OUD.

Strongly agree | Somewhat Agree | Somewhat Disagree | Strongly disagree

18. Opioid Wizard makes me feel more comfortable prescribing medications for OUD in my practice.

Strongly agree | Somewhat Agree | Somewhat Disagree | Strongly disagree

19. Using the Opioid Wizard makes it easier for me to discuss treatment options of OUD with patients and determine their preference.

Strongly agree | Somewhat Agree | Somewhat Disagree | Strongly disagree

20. Opioid Wizard helps me know when to refer patients for methadone or other specialty treatment.

Strongly agree | Somewhat Agree | Somewhat Disagree | Strongly disagree

21. When I want or need to address OUD with patients, the Opioid Wizard saves me time.

Strongly agree | Somewhat Agree | Somewhat Disagree | Strongly disagree

22. Opioid Wizard improves my office efficiency.

Strongly agree | Somewhat Agree | Somewhat Disagree | Strongly disagree

23. Time using the Opioid Wizard with patients is time well spent.

Strongly agree | Somewhat Agree | Somewhat Disagree | Strongly disagree

24. Opioid Wizard influences my treatment recommendations.

Strongly agree | Somewhat Agree | Somewhat Disagree | Strongly disagree

25. How useful are the following Opioid Wizard features?

Feature	Very useful	Moderately useful	Somewhat useful	Slightly useful	Not at all useful
	1	2	3	4	5
Screening tools (TAPS)					
Diagnosis tools (DSM criteria)					
Prescribing rescue kits (naloxone)					

Feature	Very useful	Moderately useful	Somewhat useful	Slightly useful	Not at all useful
	1	2	3	4	5
Guidance for screening for comorbidities such as alcohol use disorder, hepatitis, pregnancy					
Deciding which treatment approach is best for the patient (medications for OUD in primary care, referral to an addiction specialist, safer use, further discussion, etc.)					
Deciding between different medications for OUD (extended release injectable naltrexone vs. buprenorphine vs. methadone)					
Safety alerts for drug/drug interactions					
Urine drug screen testing reminders					

26. How could we make Opioid Wizard more useful?

_____

_____

27. Do you have any other feedback you'd like to share, or ways in which you think Opioid Wizard could be improved?

_____

Thank you for your participation. Your input is greatly appreciated!

B. Semi-Structured Interviews

A trained qualitative interviewer from within each health system will conduct all clinician, clinic staff, health system leader, and patient interviews at that site.

Clinicians and clinic staff will be recruited for interviews for the purpose of explaining and identifying barriers and facilitators to use. Specific criteria for recruitment of clinicians will depend on the implementation issue being investigated. However, a diversity of perspectives from clinicians will be sought in all data collection events.

Patients will be recruited for interviews who are referred by their PCP, diagnosed with or identified as high-risk for OUD. Because of the sensitivity of the topic of opioid use, the study team will work with a variety of stakeholders to create an acceptable recruitment method, including potentially recruiting through physicians with existing relationships with patients under treatment for OUD. A diversity of perspectives from patients will be sought in all data collection events.

Health system leaders will be recruited across sites based on their positions within the organization. The study team will recruit leaders from various levels of influence within the organizations, including high level decision makers and mid-level supervisors like clinic managers and care team leads. Selection for interviews will be as broad as possible to gain the most organizational context.

Recruitment for all interviews will be conducted by the on-site study team in a method that is acceptable in each setting. All recruitment materials will be developed and submitted for IRB review when data collection is indicated. Interview guides will be developed by the study team and submitted for IRB review and approval.

Clinician interviews will explore questions about the workflow of the OUD-CDS within the primary care setting; ease of use, areas of confusion, and potential improvements in overall usefulness for clinicians; options for overcoming barriers in primary care encounters for using the OUD-CDS; and appropriateness of the tool for clinicians' priorities in identifying and treating OUD. Clinician interviews will aim to explore and explain specific observations from the quantitative data, such as: differences between experiences of high and low clinician users of the OUD-CDS; relationship between the tool and process measures developed by the team; relationship between the tool and clinician outcomes like clinician waiver status, and/or patient outcomes like diagnosis, treatment, and post-index follow-up status. Clinician interviews will be relatively brief in nature, particularly during the active intervention phase when they will be used to learn more about problems, troubleshoot, and learn more about specific barriers.

Patient interviews will explore questions about how patients interpret the tool; reactions to having OUD raised during the primary care encounter; reactions to seeing language around their opioid use on the tool; preferences for addressing risks around opioid use in primary care settings; preferences for effective communication between patients and physicians about OUD; likelihood of accepting treatment recommendations from the OUD-CDS. Patient interviews will also aim to explore and explain specific observations from the quantitative data, such as: differences in patients identified by the OUD-CDS whose physician did or did not utilize the tool in their index encounter; differences in patients who did or did not receive post-index care or initiate treatment for OUD; differences between patients by demographics, biomedical characteristics, and co-

morbid substance use disorders. Patient interviews will be relatively specific in scope and carefully crafted for sensitivity.

All interviews will be conducted by a qualitative interviewer in a private 1-on-1 setting, either in-person or by phone. All participants will receive an informed consent document that includes all elements of consent. Consent status of all recruited participants will be documented by the study team. Interviews will be audio-recorded and submitted for verbatim transcription. Patients will receive a small incentive for each semi-structured interview. Clinicians and health care system leaders may be offered modest incentives for participation.

C. Patient Surveys

Following analysis of each round of patient interviews, each site will collect up to 130 brief surveys from patients in order to quantify the observations and conclusions drawn from the interviews. Samples for evaluation surveys will be defined and identified by the on-site study team for recruitment and data collection. Recruitment samples will be balanced by relevant patient characteristics, such as race/ethnicity, gender, or presence/absence of an OUD diagnosis in order to draw generalizations from the survey results.

The DSC will work with the Lead Node and each study site to construct a survey that will be acceptable within each care system. The survey data will be collected by the DSC electronically. The DSC will provide each study site with a list of unique survey links, one of which will be included in each invitation to a patient to respond to the survey. The survey will appear to originate within the health system where possible. All surveys will include a consent form for the respondent to agree to the collection and storage of the respondent's data prior to proceeding with the survey. Patients will receive a small incentive for survey completion.

Patient interviews will be designed first to solicit patient input on their perception about the acceptability of PCPs addressing OUD in general, feedback on the OUD-CDS in particular and how it affects this discussion, and how to better fit the tool into clinical workflows from the patient perspective. Patient survey content will then be designed based on the findings of the qualitative patient interviews, and as such, we are not submitting a draft of this survey at this time.

D. Field Notes and Observation Data

Throughout the project, each study site will maintain careful notes related to health system stakeholder engagement that include meeting notes, clinic visits, and major health system initiatives related to opioid treatment.

Each study team will contribute information from field notes to a central implementation log held and maintained by the main site. The implementation log will track major issues related to the RE-AIM constructs and contextual factors related to the care system, individual clinics, adaptations by systems and clinics, and technical changes over time in the intervention. Notes will also capture broader macro-environment issues affecting opioid treatment policy including changes in expert guidelines. Each study site will contribute updates to the implementation log on a quarterly basis.

Original primary notes will be held by the study teams as a resource to reference through the analysis process.

11.3 General Measures

11.3.1 Contact Information

We will keep a list of participating primary care clinics, their administrative leaders and their PCPs on a secure server at HealthPartners. This list will include the PCP name, primary care clinic name, phone number of the clinic and provider email address. We will also keep a separate list of healthcare system administrative leaders to engage in administrative interviews, including leader name, phone number and email address. We will keep a list of patients to engage in patient interviews and surveys, including patient name, primary care clinic name, patient phone number and patient mailing address.

11.3.2 Demographics Form

We will collect age, gender, race/ethnicity, years of practice and medical specialty (primary care vs. internal medicine) for PCP participants. Patient-level data required to assess study objectives will be collected from the EHR by the OUD-CDS and stored in a secure analytic database. Data will be collected from the EHR via the OUD-CDS tool itself, with data stored in a secure server located behind multiple HealthPartners firewalls.

11.4 Measures of Primary and Secondary Outcomes

Primary and secondary outcomes will be assessed using the data collected from the EHR via the OUD-CDS, from EHR (Clarity) data pulls, through PCP surveys and qualitative interviews, patient surveys and qualitative interviews, healthcare administrator interviews, and site implementation staff interviews. The specific outcome measures are described in **Section 7.0**.

11.5 Clinical and Safety Assessments

This intervention is being delivered by way of CDS prompts to influence provider actions to incorporate evidence-based best practice standards related to OUD. Prior to implementation, we will train all intervention PCPs and their rooming staff on the importance of helping us identify any clinician-identified safety events or near-misses that may be related to the EHR or CDS. We will systematically educate them in identification of potential safety events and near-misses and informing us of these events via use of the Feedback Tab in the CDS or email. We will also ask PCPs to notify us of any clinical situations where their clinical judgment differs from the CDS.

Use of the Feedback Tab will automatically generate an email that is sent to study team members, including PIs and programmers. The study team will then discuss this feedback and any necessary actions, and reply to the PCP to answer the question, discuss steps taken to address the issue, or gather additional information if needed to further trouble-shoot. PCPs will be asked to submit feedback any time their clinical judgment is inconsistent with the CDS tool. Additionally, the emails of study investigators will be listed on the CDS interface for providers, and PCPs will be encouraged to contact us directly with any questions or concerns if they'd rather not use the Feedback Tab in the OUD-CDS. This feedback will be provided to the DSMB twice per year or at the frequency determined by the DSMB.

12.0 TRAINING REQUIREMENTS

12.1 Overall

A comprehensive Training Plan will be developed to incorporate general training, study-specific training, and mechanisms for competency assessment. The Investigative Team is responsible for the development of a comprehensive Training Plan, instructional material, and delivery of the training (e.g., via self-study, online, webcast, or teleconference), with the team comprised of the Lead Node, Clinical Coordinating Center (CCC), Data and Statistics Center (DSC), as well as other participating nodes and subject matter experts, as applicable. PCPs who are in primary care clinics randomized to receive the OUD-CDS will be trained on how to diagnosis and manage OUD in primary care, use of the OUD-CDS, and the importance of using the Feedback Tab to let the study team know of any issues or questions. Traditionally, we have completed such trainings at in-person lunch meetings with clinic personnel, but will also consider other training modalities, such as web-based trainings or teleconferences, depending on the standard training practices at partner sites and clinic leadership preference.

Study staff will be trained as specified in the Study Training Plan and are required to complete institutionally required training per their research site, IRB(s), and authorities with regulatory oversight. Training will include Human Subject Protection (HSP) and Good Clinical Practice (GCP), as well as protocol-specific training. Tracking of training completion for individual staff as prescribed for assigned study role(s) will be documented, endorsed by the site Principal Investigator and the Lead Node, and audited by the CCC. As changes occur in the prescribed training, the Training Plan and training documentation tracking forms will be amended to reflect these adjustments.

13.0 STATISTICAL DESIGN AND ANALYSES

13.1 General Design

13.1.1 Study Hypotheses

H1.1: Patients previously undiagnosed with OUD but identified as high risk by the OUD-CDS at an index visit will be more likely to receive an OUD diagnosis (in the problem list or as an ICD-10 visit code) in intervention clinics than UC clinics within 30 days post-index.

H1.2: Patients previously diagnosed with OUD or identified as high risk by the OUD-CDS at an index visit will be more likely to have naloxone rescue kits ordered in the intervention clinics than in the UC clinics within 30 days post-index.

H2.1: Patients identified as having OUD or as being at high-risk for OUD by the OUD-CDS at an index visit will be more likely to have MOUD orders or referral for OUD treatment within 30 days post-index in intervention clinics than in UC clinics.

H2.2: Patients identified as having OUD or as being at high-risk for OUD by the OUD-CDS at an index visit will have significantly more days covered by a MOUD prescription at 90 days post-index in intervention clinics than in UC clinics.

H3.1: Patients with OUD or identified as high-risk for OUD by the OUD-CDS who are cared for in intervention clinics will have significantly fewer post-index ED visits during the observation period (i.e., the period between each patient's index date and last observation) compared to patients cared for in UC clinics.

H3.2: Patients with OUD or identified as high-risk for OUD by the OUD-CDS who are cared for in intervention clinics will have significantly fewer post-index hospitalizations during the observation period compared to patients cared for in UC clinics.

H4.1: After controlling for demographics, baseline clinical status and prior costs of care, patients with OUD or identified as high risk for OUD by the OUD-CDS will have lower healthcare costs in intervention compared to UC clinics during the observation period (i.e., savings from lower ED visits and hospitalizations will outweigh increased costs of OUD treatment and naloxone rescue kits and OUD-CDS implementation and maintenance).

13.1.2 Primary and Secondary Outcomes (Endpoints)

Primary outcome measures will include:

1. OUD diagnosis (in the problem list or as an ICD-10 visit code) within 30 days of index visit for patients identified by the OUD-CDS as being at high risk of OU
2. Naloxone prescription within 30 days of index visit for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
3. MOUD orders or referral to OUD treatment within 30 days of index visit for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
4. Total days covered by an MOUD prescription in the 90 days after index visit for patients with OUD or identified by the OUD-CDS as being at high risk for OUD

Secondary outcome measures will include:

1. OUD diagnosis (in the problem list or as an ICD-10 visit code) at index or within 90 days of index visit for patients identified by the OUD-CDS as being at high risk of OUD
2. Naloxone prescription at index or within 90 days of index visit for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
3. MOUD orders or referral to OUD treatment at index or within 90 days of index visit for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
4. Number of ED visits during the observation period for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
5. Number of hospitalizations during the observation period for patients with OUD or identified by the OUD-CDS as being at high risk for OUD
6. Healthcare costs during the observation period for patients with OUD or identified by the OUD-CDS as being at high risk for OUD, compared with healthcare costs over the same interval preceding the observation period
7. Cost of OUD-CDS implementation and maintenance
8. All-cause mortality rates during the observation period for patients at high risk of OUD
9. Fatal and non-fatal opioid overdoses during the observation period for patients at high risk of OUD
10. Rates of OUD-CDS use in intervention clinics
11. PCP ratings of confidence in treating patients with OUD prior to go-live date and 9-months following go-live date
12. Intervention clinic PCP ratings of satisfaction and acceptability of the OUD-CDS at 9 months following go-live date

Exploratory outcome measures may include:

1. Number of non-waivered PCPs becoming buprenorphine waivered during the intervention period, assessed via health system administrative data
2. Number of buprenorphine prescriptions written by waivered PCPs during the intervention period
3. PCP ratings of likelihood to prescribe buprenorphine for patients with OUD should no waiver be required, measured prior to go-live dates and 9-months following go-live dates
4. Adherence to therapy during the observation period, assessed via Clarity and claims data
5. Number of patients diagnosed with OUD screened for mental health comorbidities and infectious diseases during the observation period

13.1.3 Recruitment

COMPUTE 2.0 will be conducted at a minimum of 30 primary care clinics within 3 care systems that are geographically dispersed and will include a racially, ethnically and socioeconomically diverse population. Site 1 is HealthPartners, which was the sole site for the COMPUTE 1.0 pilot study, while Site 2 is Geisinger and Site 3 is Essentia. A minimum of 10 primary care clinics to be included per site will be selected in partnership with site PIs and primary care leadership at each site, taking into consideration such factors as overall clinic size, number of waivered PCPs, and baseline prevalence of diagnosed OUD. Clinics will be randomized equally within care system

and balanced on pre-randomization outcomes, such as the percentage of study-eligible patients with diagnosed OUD, and on clinic characteristics that may enhance or impede intervention uptake and adherence, such as the number of waivered PCPs (see **Section 10.2**).

PCPs who practice at randomized clinics will be asked to complete surveys prior to go-live date and 9-months after go-live date assessing their comfort and confidence treating patients with OUD, and among providers in intervention clinics their perceptions of the OUD-CDS. The DSC will work with the Lead Node and each study site to construct a survey that will be acceptable within each care system. The survey data will be collected by the DSC electronically. Samples for PCP surveys will be identified by the on-site study teams for recruitment and data collection. The DSC will provide each study site with a list of unique survey links, one of which will be included in each invitation to a PCP to respond to the survey. The survey will appear to originate within the health system where possible. All surveys will include a consent form which will allow the respondent to agree to the collection and storage of the respondent's data prior to proceeding with the survey. Clinicians may be offered an incentive for participation.

A sample of patients who have been diagnosed with OUD, have been identified as being at high risk for OUD or opioid overdose, or referred by a PCP will be recruited to participate in surveys and interviews via a mailed or emailed invitation based on standard processes at each site. Samples for evaluation surveys will be defined and identified by the on-site study team for recruitment and data collection. Survey recruitment samples will be balanced by relevant patient characteristics, such as race/ethnicity, gender, or presence/absence of an OUD diagnosis in order to draw generalizations from the survey results. The DSC will work with the Lead Node and each study site to construct a survey that will be acceptable within each care system. The survey data will be collected by the DSC electronically. The DSC will provide each study site with a list of unique survey links, one of which will be included in each invitation to a patient to respond to the survey. The survey will appear to originate within the health system where possible. All surveys will include an informed consent document with the elements of consent for the respondent to agree to prior to proceeding with the survey. Patients will receive a small incentive for survey completion.

Clinic and administrative leaders will be identified as potential candidates for interviews in conjunction with site investigators and healthcare system leadership. Leaders will be emailed an invitation to participate in a phone or in-person interview, and leaders will complete verbal consent to participate at the beginning of the phone interview.

13.1.4 Randomization and Factors for Stratification

The OUD-CDS software is a system-level intervention comprised of 1) a passively operating web service that gathers, analyzes and retains information pertinent to every web service call, and 2) a user interface that presents a summary of algorithm results to front end users. The web service documents every web service call made by all front-end users in all participating locations so that data pertinent to all targeted visits from all eligible and enrolled patients will be identically collected and available in both treatment arms. The user interface will function as the intervention delivery vehicle and therefore be operative only in intervention locations. Intervention or Control designation will vary randomly by clinic. The OUD-CDS web service will therefore operate

passively in all participating clinics but the user interface will only be turned on in clinics that are randomly assigned to the intervention treatment group.

To the extent that patients tend to receive most of their care over time at a single clinic, and that clinicians tend to practice at a single clinic, it is reasonable to assert that the risk of intervention contamination across clinics is low. However, because it is common for patients to see more than one clinician in a clinic location over time, and for clinicians within a clinic location to discuss aspects of care delivery with each other, the risk of intervention contamination within clinics is rather high. Randomizing by clinic rather than by PCP or patient will minimize risk of intervention contamination.

Generally speaking, randomization should balance treatment groups on factors that enhance or impede intervention uptake and adherence, that are related to and including study outcomes, and on any other unmeasured factors that may affect statistical power. However, the likelihood that factors related to these considerations are balanced may be diminished in cluster-randomized trials due to relatively few randomized units.[33, 34] Covariate constrained randomization will be implemented to balance treatment groups across the study and within health care systems (strata) on factors related to study outcomes, implementation of the intervention, and potential treatment modifiers.

Potential balancing factors include:

- n of waivered providers
- n of adult patients at clinic
- % of adult patients with government sponsored insurance
- % of adult patients who are non-Hispanic White
- % of all patients at high risk for OUD
- % of patients at high risk for OUD provided a with naloxone rescue kit
- % of all patients with diagnosed OUD
- % of all patients with diagnosed OUD with a current MOUD

Each patient will be assigned to the clinic in which his or her first visit that is eligible for the OUD-CDS intervention (i.e., index visit) takes place, and as such will be assigned to the treatment group to which their clinic was randomly assigned. Post-index visits may take place in the same or different clinics or treatment groups relative to the index visit and may or may not be eligible for the OUD-CDS to offer treatment recommendations. In keeping with an intent-to-treat principle, all index and post-index visits and outcome measures for each patient will be attributed to the treatment group assignment of the clinic where the index visit took place.

Further details regarding the randomization procedures including the final balancing factors included in the randomization are provided in a separate study randomization plan.

13.1.5 Prediction Models

Aims 1 through 3 pertain to the effectiveness of the OUD-CDS intervention relative to UC, predicting that it will increase diagnosis, naloxone prescribing, and access to MOUD, and decrease ED visits and inpatient stays. These hypotheses will be tested using generalized linear mixed models to account for clustering of outcomes within eligible patients and randomized clinics, or using generalized estimating equations to compare event rates. Outcomes will be normalized via distribution-appropriate link functions (e.g., logistic-Normal, Poisson-Normal).

Clinic-randomized treatment group, care system and other predictors will be treated as fixed effects.

13.2 Rationale for Sample Size and Statistical Power

13.2.1 Projected Number of Sites

At least 30 primary care clinics at three participating healthcare systems (i.e., at least 10 primary care clinics per healthcare system) are expected to participate in this study.

13.2.2 Projected Number of Participants per Site

There must be at least 50 patients with or at high risk for OUD at an index visit at a randomized clinic for it to be included in the analyses. Based on the number of patients with study-eligible visits in the COMPUTE 1.0 pilot study, we expect this will be a low threshold for clinics to attain. The COMPUTE 1.0 intervention was implemented for six months among 55 randomized providers who practiced in 30 clinics. During that time, these providers saw between 14 and 137 patients (provider median = 77; 37-412 patients per clinic, clinic median = 163) who were eligible for the pilot OUD-CDS intervention. To the extent the COMPUTE 2.0 intervention is expected to collect outcome data on patients for 19 to 31 months in the randomized clinics, and study-eligible patients will be seen by all clinic providers, it is plausible to expect that 1,000 study-eligible patients could have index visits at many clinics.

13.2.2.1 Statistical Power

A preliminary power analysis was conducted to estimate the minimum detectable difference in the likelihood of OUD diagnosis (H1.1), naloxone rescue kit order (H1.2) and MOUD order or referral for treatment (H2.2) within 30 days of the index visit, and the number of days covered by a MOUD prescription in the 90 days post-index (H2.2) among patients cared for in OUD-CDS relative to UC clinics (see **Section 13.4**). The power analysis relied on conservative assumptions regarding the numbers of randomized clinics (10, 30, 50) and of eligible patients (50 or 100 per clinic); a range of clinic intraclass correlations consistent with those observed for other process measures at HealthPartners (i.e., ICC_{clin} = 0.01, 0.03, 0.05); and central tendency estimates for the outcomes (2%, 5%, 10% and 20% or 70, 50, 30 days not covered in UC). Power estimates will be updated after Sites 2 and 3 are selected and preliminary data to inform analysis assumptions become available.

Effect size estimates for the binary outcomes were calculated using the NIH group randomized trial sample size calculator.[48] The difference in days covered was estimated using the Poisson regression module of PASS 11 software[49] after calculating an effective sample size (i.e., N_{eff} = (n clinics*m patients per clinic) / (1+(m-1)*ICC_{clin})). In addition, the Poisson model power analysis was conducted to estimate the minimally detectable decrease in days NOT covered in the 90 days to post-index among OUD-CDS relative to UC patients to ensure that the estimated days in both groups remained between 0 and 90 days.

Table 3 summarizes the minimum detectable increases in outcome rates among OUD-CDS relative to UC patients given the aforementioned assumptions. Assuming 30 randomized clinics with 50 high risk patients each, that 5% of UC patients have an OUD diagnosis within 30 days of their index visit and ICC_{clin} = 0.03, the H1.1 analysis would be powered (power=0.80, α_2 = 0.05) to detect a difference if ≥11.35% (odds ratio = 2.43) of OUD-CDS patients have an OUD diagnosis within 30 days of their index visit. For an event occurring among 10% of UC patients given the

same assumptions otherwise, an analysis would be powered to detect a difference if it occurs among ≥ 18.12% (odds ratio = 1.99) of OUD-CDS patients. Having more patients per clinic (e.g., 30 clinics * 100 patients each = 3000 patients) results in a smaller detectable effect size (i.e., 17.18 OUD-CDS vs. 10% UC; odds ratio = 1.87) although randomizing more than the minimum 30 clinics (e.g., 50 clinics * 50 patients each = 2500 patients) would reduce the minimum detectable effect (i.e., 16.02 OUD-CDS vs. 10% UC; odds ratio = 1.72) further with fewer patients. Table 3 also demonstrates that site-specific analyses of the OUD-CDS treatment effect would be sufficiently powered to detect only large effect sizes (e.g., 26.73% vs. 10%; odds ratio = 3.28) with 30 randomized clinics.

Table 3. Minimum detectable increase in the proportion of OUD-CDS relative to UC patients to experience the H1.1, H1.2 and H2.1 outcomes at the index visit, assuming n=(50, 100) patients per clinic, m=(10, 30, 50) randomized clinics, ICC_{clin}=(.01, .03, .05) and 2%, 5%, 10%, 20% outcome rates in UC.

UC %	2%	5%	10%	20%	2%	5%	10%	20%
	n patients / clinic = 50				n patients / clinic = 100			
ICC_{clin}	m=10 clinics (minimum site-specific)				m=10 clinics (minimum site-specific)			
0.05	15.86	21.97	30.19	43.77	14.52	20.52	28.60	41.98
0.03	12.89	18.54	*26.73*	40.08	12.07	16.91	24.56	37.79
0.01	9.86	15.11	22.62	35.51	8.42	13.08	20.08	32.50
ICC_{clin}	m=30 clinics (minimum study-wide)				m=30 clinics (minimum study-wide)			
0.05	8.01	12.89	19.84	32.10	7.32	12.15	19.03	31.18
0.03	6.85	*11.35*	*18.12*	30.52	6.12	10.62	*17.18*	29.08
0.01	5.46	9.80	16.22	27.80	4.74	8.80	14.93	26.28
ICC_{clin}	m=50 clinics				m=50 clinics			
0.05	6.14	10.73	17.27	29.09	5.85	10.17	16.66	28.41
0.03	5.40	9.64	*16.02*	27.62	4.95	9.10	15.33	26.8
0.01	4.45	8.49	14.59	25.86	3.94	7.84	13.68	24.75

Table 4 provides a comparable summary for the H2.2 outcome, days covered by a MOUD prescription in the 90 days post-index. The inverse of the H2.2 outcome was used to calculate the minimum detectable difference in MOUD coverage days to ensure that estimated decreases in days not covered (or, increases in days covered) remained between 0 and 90 days. Continuing with the assumptions from the prior examples, the H2.2 analysis would be sufficiently powered to detect a decrease in days not covered by a MOUD if UC patients had 50 of their 90 post-index days uncovered (40 covered) but OUD-CDS patients had at least 37.0 uncovered (53.0 covered) days.

Table 4. Minimum detectable decrease in 90 days post-index without a MOUD prescription among OUD-CDS relative to UC patients, assuming n=(50, 100) patients per clinic, m=(10, 30, 50) randomized clinics, ICC_{clin}=(.01, .03, .05) and 30, 50, 70 days not covered in UC.

UC	RR	30	50	70	RR	30	50	70
	n patients / clinic = 50				n patients / clinic = 100			
ICC_{clin}	m=10 clinics (minimum site-specific)				m=10 clinics (minimum site-specific)			
0.05	0.615	18.5	30.8	43.1	0.638	19.1	31.9	44.7
0.03	0.665	19.9	33.4	46.5	0.695	20.9	34.8	48.6
0.01	0.731	21.9	36.4	51.2	0.775	23.2	38.7	54.2
ICC_{clin}	m=30 clinics (minimum study-wide)				m=30 clinics (minimum study-wide)			
0.05	0.760	22.8	38.0	53.2	0.775	23.3	38.8	54.3
0.03	0.739	22.2	*37.0*	51.7	0.813	24.4	40.6	56.9
0.01	0.836	25.1	41.8	58.5	0.864	25.9	43.2	60.5
ICC_{clin}	m=50 clinics				m=50 clinics			
0.05	0.809	24.3	40.5	56.6	0.822	24.7	41.1	57.5

0.03	0.836	25.1	41.8	58.6	0.852	25.6	42.6	59.7
0.01	0.871	26.1	43.6	61.0	0.893	26.8	44.7	62.5

13.3 Statistical Methods for Primary and Secondary Outcomes

This section provides an overview of the statistical methods to be employed in testing the primary and secondary outcomes. A more detailed description of the analysis may be found in the Statistical Analysis Plan. The Statistical Analysis Plan will provide more clarity about the underlying assumptions and methodological decisions regarding primary outcome analyses, including the extent to which either supplement alters the treatment effect.

Hypotheses for Aims 1 and 2 predict that the OUD-CDS intervention will increase the likelihood that patients at high risk of OUD are diagnosed with OUD (H1.1); and that among those at high risk or diagnosed with OUD it will increase the likelihoods that a naloxone rescue kit is ordered (H1.2) and that MOUD is ordered or the patient is referred to a provider who can order MOUD (H2.1), and the number of days covered by an MOUD prescription (H2.2). The hypotheses from Aims 1 and 2 will be tested using generalized linear mixed models so that the likelihood or counts of outcomes may be accurately estimated among OUD-CDS relative to UC clinics, accounting for the clustering of patients within randomized clinics. Binary outcomes (H1.1, H1.2, H2.1) will be normalized using a logistic-Normal link function, while it is anticipated that the count outcome (H2.2) will be normalized using a Poisson-Normal link function. The model will estimate fixed effects of OUD-CDS, care system and other covariates on outcomes, and random intercepts for clinics and patients (H1.1, H1.2, H2.1) or for clinics (H2.2).

Hypotheses for Aim 3 predict fewer ED visits (H3.1) and inpatient stays (H3.2) during the observation period of patients receiving care in the OUD-CDS relative to UC clinics. The rate at which each of these outcomes occurs per patient-year will be compared across clinics using generalized estimating equations. Clinic-aggregated counts of ED visits and inpatient stays will be normalized using a Poisson-Normal link function, and the intercept offset by the log of patient-years within the clinic. The model will estimate fixed effects of OUD-CDS, care system and other covariates on the rate of each outcome per patient-year. Should it be feasible, we will also collect and count ED visits and inpatient stays that occurred in the year prior to each patient's index visit so that treatment group differences in pre-post changes in event rates can be quantified (i.e., treatment by time interaction).

Hypotheses for Aim 4 predict lower healthcare costs and the identification and mitigation of barriers and identification of facilitators to OUD-CDS implementation and uptake. **Analysis of costs** for this aim will include delivery costs of the OUD-CDS and incremental medical care costs attributable to the intervention, defined from the health system perspective. Intervention costs may include resources used for implementation, maintenance, compensation, and PCP and staff training – which may be assessed by interviews/surveys with implementation site staff or study resource use documentation, as appropriate – but will exclude research, development, and measurement costs, using standard micro-cost accounting methods and nationally-representative pricing of inputs. Medical care costs will include all prescribed medications and clinical inpatient, emergency, outpatient, and skilled nursing facility services incurred in the pre- and post-index observation periods by participants in each study group, as indicated by insurance claims and clinical encounter data. The study sample for the cost analysis will be participants who have continuous insurance coverage during the study period, including pharmacy benefits. This sample

will be compared to patients without continuous insurance coverage to assess representativeness and comparative completeness of utilization measurement in comparison to all study participants.

Paid amounts for medical claims that are specific to medical groups and insurance plans may provide a biased view of costs between pre- and post-intervention periods. To address this, claims will be converted to dollar amounts using Total Care Relative Resource Values ™ (TCRRVs), which are a nationally standardized set of measures that have been endorsed by the National Quality Forum[50] and are derived from Centers for Medicare and Medicaid Services (CMS) relative value units (RVUs). TCRRVs extend CMS RVU measures to include utilization categories, such as laboratory services and medications, which do not have CMS RVU weights.[51] Inpatient costs are calculated by applying TCRRVs to the diagnosis-related group classification and length of stay of the hospitalization.

Standard health econometric and specification testing methods will be used to assess the incremental differences in healthcare costs between study groups [1, 2, 39]. Specifically, healthcare care costs will be analyzed using a generalized hierarchical model with a time x study group interaction term that can account for clinic-level clustering and the correlation in each subjects' repeated measures of costs over time (i.e., pre-index and post-index). Demographics and baseline clinical status will be controlled for based on randomization imbalances and model fit criteria. The marginal effect of being assigned to an intervention clinic will provide an estimate of the incremental medical cost associated with the OUD-CDS intervention. To account for the non-normality in costs, the distribution family will be specified appropriately, such as by using the modified Park test,[2] and the goodness of fit for the specified link function will be tested, such as by using modified Hosmer and Lemeshow and Pregibon link tests.[53, 54] Confidence intervals will be estimated using heteroscedasticity-robust estimation methods.[55]

Mixed method data analysis for Aim 5 will occur rapidly as data are collected, so that new information can support decision making about revisions in the implementation plan and adaptations as the study proceeds. All data analysis and subsequent conclusions and decisions made during live implementation will be carefully documented.

After the implementation phase is complete at all sites, monitoring data, survey data, and qualitative data from all sites will be triangulated to draw conclusions about the barriers, facilitators, adaptations, and recommendations for future dissemination of the OUD-CDS tool.

13.3.1 Qualitative Data Analysis

All interview data (from patients, PCPs and leaders) will be analyzed in two phases by a team consisting of the interviewers and analysts from each of the sites:

1. Small samples will be reviewed immediately without coding to identify specific intervention problems needing prompt attention and revision in implementation approach.
2. As larger samples are created, we will use a more standard content analysis employing an iterative data-reduction method.[56]

A draft codebook will be developed based on the structure and content of the interview guide. That will be revised during application in early interviews by the analysis group so that eventually

coding can be performed by pairs of analysts while the larger analytic group can focus on the identification of categories, themes, and patterns emerging from the data. The main analytic purpose is to identify the clinic, PCP and patient barriers and facilitators to consistent effective use of the OUD-CDS.[57] Classification schemes and typologies will be used to identify and develop themes, concepts, and patterns. Coding and managing qualitative analyses will be conducted using appropriate software.

We will maintain a data codebook and audit trail in order to map decision points in the analysis. Individual interviews that do not fit evolving patterns in the data will get special attention. The analysis team will work to agree on final themes and patterns in the data and interview data will be triangulated with other data sources. These themes and patterns will then be developed into recommendations for larger, less immediate adaptations in the use of the OUD-CDS that can then be tested in subsequent interviews with key informants.

13.3.2 PCP Survey Data Analysis

PCP survey analyses will compare providers' pre- and post-implementation reports of confidence in treating patients with OUD and other items included in both PCP surveys; and to assess intervention providers' post-implementation ratings of satisfaction and acceptability of the OUD-CDS. Generalized linear mixed models will compare pre-post PCP ratings to account for repeated survey measures from PCPs and to ensure all PCP ratings are included in the estimated changes in ratings. Changes in PCP ratings may vary as a function of contextual factors or PCP characteristics. In secondary analyses of the PCP ratings, care system indicators (Site 1, Site 2, Site 3), clinic (e.g., proportion of primary care patients eligible for OUD-CDS, proportion of clinic patients with government-sponsored insurance), and provider (e.g., waiver status, number of patients eligible for OUD-CDS) characteristics may be considered as main effects or in interaction with each other or the treatment group indicator to assess their relationship with pre-post changes in survey outcomes. Provider ratings may also be used to represent provider characteristics that may modify the OUD-CDS treatment effectiveness.

13.3.3 Patient Survey Data Analysis

Patient survey analyses will be descriptive to assess the extent to which themes identified in patient interviews are confirmed in a larger sample, and to identify correlates between these themes and other patient characteristics, such as racial/ethnic group, age group, or being at high risk for OUD vs. having diagnosed OUD.

Secondary outcomes analyses will follow the same logic as the primary outcomes analyses. Secondary outcomes that quantify person-based outcomes (e.g., MOUD maintenance and adherence) will be analyzed using generalized linear mixed models while those that represent population-averaged event rates (e.g., all-cause death rates, fatal and non-fatal opioid overdose rates) will be analyzed using generalized estimating equations.

13.4 Significance Testing

The H1.1, H1.2 and H2.1 outcomes will be assessed 3 times for each patient – at the index visit (0 days), and 30 (for primary outcomes) and 90 days post-index. Outcomes that occur at an index visit will be coded as also having occurred by days 30 and 90. Similarly, outcomes that occur between days 1 and 30 will be coded as having occurred by days 30 and 90; and those occurring

between days 31 and 90 will be coded as having occurred by day 90. We expect that the documented actions that providers take will be overwhelmingly attributable to the index visit. Some actions that providers initiate at the index visit, such as placing a treatment referral order, may not be complete until considerations related to safety or availability are addressed. The primary outcome for H1.1, H1.2 and H2.1 will be assessed at 30 days so that these actions, likely initiated at the index visit, may be completed prior to assessing the outcome. It is possible that outcomes will not be documented for patients who have post-index visits within 90 days at non-participating clinics. We assume that these eventualities will be rare and equally likely across treatment groups.

Because virtually all of the information pertinent to the H1.1, H1.2 and H2.1 outcomes will be captured by the day 30 measure, the primary hypothesis test for these models will compare the likelihood of the day 30 outcome by treatment group. The primary hypothesis test for the H2.2 outcome will compare the likelihood of the day 90 outcome by treatment group. These comparisons will be evaluated using a two-sided test with a Type I error rate of 5%. Comparisons at other time points will aid understanding of how relative differences in OUD-CDS versus UC settings may increase or decrease in the short term. For example, OUD-CDS might initiate a course of provider actions that otherwise would not occur (increase) or merely hasten action that eventually takes place in UC settings (decrease).

The Aim 3 outcomes represent counts of events that accrue over the post-index observation periods. The event rates in OUD-CDS versus UC clinics will be evaluated using a two-sided test with a Type I error rate of 5%.

For Aim 4, Hypothesis 4.1, the marginal effect of being assigned to an intervention clinic will provide an estimate of the incremental medical cost associated with the OUD-CDS intervention. Analyses will be 2-sided, and p-values of less than .05 will be considered statistically significant. Confidence intervals will be estimated using heteroscedasticity-robust estimation methods.[55]

There are several secondary outcomes; however, multiple comparisons will not be adjusted for since these are not part of the study's primary objective.

13.5 Interim Analysis

There are no planned interim analyses.

13.6 Exploratory Analysis

Treatment effectiveness may vary as a function of contextual as well as patient factors. In secondary analyses of the primary outcomes, care system indicators (Site 1, Site 2, Site 3), clinic (e.g., proportion of primary care patients eligible for OUD-CDS, proportion of clinic patients with government-sponsored insurance), and provider (e.g., waiver status, number of patients eligible for OUD-CDS, confidence in treating patients with OUD, intent to prescribe buprenorphine if waiver no longer required) characteristics may be added to the primary model as main effects and in interaction with the treatment group indicator to assess treatment heterogeneity due to contextual factors. Patient characteristics (e.g., race, ethnicity, age, estimated neighborhood income and education, documented heroin vs. oral opioid use) may be similarly added to assess treatment heterogeneity due to patient factors.

13.7 Missing Data and Dropouts

We expect person-based missingness to be extremely rare. Patients are unlikely to be aware that their data are being used for this research. They will not be consented and are unlikely to request that their data be excluded from analyses. Only patients who have requested that their data not be used for research and appear on site-maintained opt out lists will be excluded.

The primary data source for the Aim 1 through 3 hypotheses will be gathered from EHR-based data repositories at each participating site. The stored EHR data elements required for calculating the primary and secondary outcomes are extracted from live production tables. Medical care costs for Aim 4 will come from administrative claims systems that are relied upon for reimbursement of medical care services. The absence of documentation of a care process, vital sign, or medication should not be interpreted as a missing value but rather as indicative of a care process or test not having been performed or medication not prescribed within the health system. Likewise, absence of utilization indicated by billing claims almost always indicates that the utilization (such as a hospitalization) did not occur. Truly missing field-based observations (e.g., OUD diagnosis assigned, action not observed) will be extremely rare, undetectable and assumed to be missing at random.

13.8 Demographic and Baseline Characteristics

Demographic and clinical variables available in the EHR at the index visits will be summarized for all enrolled study participants, overall and by site and treatment group. Descriptive summaries of the distribution of continuous baseline variables will be presented with percentiles (median, 25th and 75th percentiles), and with mean and standard deviation. Categorical variables will be summarized in terms of frequencies and percentages.

13.9 Safety Analysis

We will assess the rates of ED use, hospitalization and opioid overdoses that occur in intervention and control clinics during each patient's observation period. The rate at which each of these outcomes occurs per patient-year will be compared across clinics using generalized estimating equations. Clinic-aggregated counts of ED visits and inpatient stays will be normalized using a Poisson-Normal link function, and the intercept offset by the log of patient-years within the clinic. The model will estimate fixed effects of OUD-CDS, care system and other covariates on the rate of each outcome per patient-year. Should it be feasible, we will also collect and estimate the rate at which these events occurred in the year prior to each patient's index visit so that treatment group differences in pre-post changes in event rates can be quantified (i.e., treatment by time interaction).

14.0 REGULATORY COMPLIANCE, REPORTING and MONITORING

14.1 Statement of Compliance

This study will be conducted in accordance with the current version of the protocol, in full conformity with the ethical principles outlined in the Declaration of Helsinki, the Protection of Human Subjects described in the International Council for Harmonisation (ICH) GCP Guidelines, applicable United States Code of Federal Regulations (CFR), the NIDA Terms and Conditions of Award, and all other applicable state, local and federal regulatory requirements. The PIs will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants. An Operations Manual will be provided as a study reference guide and study quality assurance tool.

14.2 Institutional Review Board Approval

Prior to initiating the study, participating site investigators will obtain written IRB approval from the IRB to conduct the study at their respective sites, which will include approval of the study protocol. If changes to the study protocol become necessary, protocol amendments will be submitted in writing by the investigators for IRB approval prior to implementation. In addition, IRBs will approve all consent forms, recruitment materials, and any materials given to the participant, and any changes made to these documents throughout study implementation. For changes to the consent form, a decision will be made regarding whether previously consented participants need to be re-consented. IRB continuing review will be performed annually, or at a greater frequency contingent upon the complexity and risk of the study. Each Site PI is responsible for maintaining copies of all current IRB approval notices, IRB-approved consent documents, and approval for all protocol modifications. These materials must be received by the investigator prior to the initiation of research activities at the site and must be available at any time for audit. Unanticipated problems involving risk to study participants will be promptly reported to and reviewed by the IRB of record, according to its usual procedures.

HealthPartners will serve as Site 1, and as such, the HealthPartners IRB will serve as the central IRB for this study. The IRBs at Sites 2 and 3 will be expected to cede to the HealthPartners IRB and enter into reliance/authorization agreements for Protocol CTN 0095. The HealthPartners IRB will provide study oversight in accordance with 45 CFR 46. HealthPartners IRB will follow written procedures for reporting its findings and actions to appropriate officials at each participating institution. Of note, it is possible a partner site may meet Exception Criteria to the NIH sIRB (single IRB) Policy and may not utilize the IRB of Record.

14.3 Informed Consent

14.3.1 OUD-CDS Implementation

We will request a waiver [or alteration] of informed consent of patients and PCPs from the IRB of record for this study to implement and run the OUD-CDS in primary care clinics. In accordance with applicable federal regulations (45 CFR 46.116(f)), the study protocol meets the following required criteria as defined in 45 CFR 46.116(f)(3)):

- The research involves no more than minimal risk to the subjects;
- The research could not practicably be carried out without the requested waiver or alteration;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
- Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

COMPUTE 2.0 uses secondary observational data to evaluate outcomes that result from primary care clinics randomized to receive or not receive access to the OUD-CDS. Use of these observational data pose no more than minimal risk of harm to subjects, with the risk chiefly being loss of confidentiality of data. The risk of using these data is no greater than the risk of routine uses of healthcare data for quality improvement by the health systems. Subjects' access to healthcare or healthcare benefits will not be affected by this study.

The primary objective of this study could not be achieved if only consenting a sub-sample of patients were included. Moreover, to identify these subjects and conduct outreach to obtain signed authorization would greatly increase the risk of breach of confidentiality. Additionally, we estimate our patient enrollment numbers will exceed 10,000 across the three participating healthcare systems. The study could not therefore be practically carried out if consent were required.

The integration of the OUD-CDS into primary care clinics involves no more than minimal risk to PCPs and patients, as the OUD-CDS is meant to help PCPs achieve the standard of care for OUD, not to change the standard of care. Historically this waiver has been granted by our and other participating site IRBs for similar CDS studies.

14.3.2 Patient, PCP and Health System Leader Interviews and Surveys

All patients, PCPs and health system leaders will be consented to participate in any interviews or surveys. The informed consent process is a means of providing study information to each prospective participant and allows for an informed decision about participation in the study. The informed consent forms will include all of the required elements of informed consent. Every interview or survey participant is required to give consent verbally, electronically, or physically (via study staff prior to in-person interviews) prior to the initiation of any interview or survey. Every participant providing consent verbally or electronically will have the opportunity to obtain a hard copy of the consent form.

Prior to informed consent, research staff will provide a detailed description of the study and interview or survey to the potential participant and provide a copy of the consent to read. If the participant is interested in participating in the interview or survey, he or she will have the opportunity to ask any questions related to participation.

The informed consent forms will be updated or revised whenever important new safety information is available or whenever the protocol is amended in a way that may affect participants' participation in the trial. Participants will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason, without penalty. Individuals who refuse to participate in interviews or surveys or who withdraw will be treated without prejudice. Study

sites will be responsible for maintaining signed consent forms as source documents for quality assurance (QA) review and regulatory compliance in a manner that is in compliance with the overseeing IRB and its institutional policies.

14.4 Quality Assurance Monitoring

In accordance with federal regulations, the study sponsor is responsible for ensuring proper monitoring of an investigation and ensuring that the investigation is conducted in accordance with the protocol. Qualified monitors will oversee aspects of site conformity to make certain the site staff is operating within the confines of the protocol, and in accordance with GCP. This includes but is not limited to protocol compliance, documentation auditing, and ensuring the informed consent process is being correctly followed and documented. Non-conformity with protocol and federal regulations will be reported as a protocol deviation and submitted to the study sponsor and study IRB of record for further review.

14.5 Participant and Data Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor and funding agency, and will be maintained in accordance with all applicable federal regulations and/or state/Commonwealth law and regulations. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency and the participant.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the investigator. The clinical study site will permit access to such records.

Participant records will be held confidential by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as denoted in **Section 14.11, Records Retention and Requirements**.

By signing the protocol signature page, the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB/Privacy Board, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

14.5.1 Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical,

behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see https://humansubjects.nih.gov/coc/index). This protects participants from disclosure of sensitive information (e.g., drug use). It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

14.5.2 Health Insurance Portability and Accountability Act (HIPAA)

Study sites may be required by their institutions to obtain authorization from participants for use of protected health information. Sites will be responsible for communicating with the IRBs or Privacy Boards of record and obtaining the appropriate approvals or waivers to be in regulatory compliance. Releases of participant identifying information that are permitted by the HIPAA regulations, but which are prohibited by other applicable federal regulations and/or state/Commonwealth law and regulation, are prohibited.

14.6 Investigator Assurances

Each site must file (or have previously filed) a Federalwide Assurance (FWA) with the HHS Office for Human Research Protection (OHRP) setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects in alignment with 45 CFR 46, Subpart A, with documentation sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103). Prior to initiating the study, the PI at each study site will sign a protocol signature page and investigator agreement, providing assurances that the study will be performed according to the standards stipulated therein.

14.6.1 Financial Disclosure/Conflict of Interest

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will confirm to the sponsor annually that they have met their institutional financial disclosure requirements.

14.7 Clinical Monitoring

Investigators may host periodic visits by NIDA contract monitors who will examine whether study procedures are conducted appropriately and that study data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulations. These monitors will audit, at mutually agreed upon times, regulatory documents, case report forms (CRFs), informed consent forms and corresponding source documents for each participant. Monitors will have the opportunity and ability to review any study-associated document or file.

NIDA-contracted monitors will assess whether submitted data are accurate and in agreement with source documentation and will also review regulatory/essential documents such as

correspondence with the IRB. Areas of particular concern will be participant informed consent forms, protocol adherence, reported safety events and corresponding assessments, and PI oversight and involvement in the trial. Reports will be prepared following the visit and forwarded to the site principal investigator, the lead investigator and NIDA CCTN.

Qualified node personnel (Node QA monitors) or other designated parties will provide site management for each site during the trial. Node QA staff or other designated parties will audit source documentation, including informed consent forms and HIPAA forms. This will take place as specified by the local protocol team, node PI or lead team and will occur as often as needed to help prevent, detect, and correct problems at the study sites. Node QA personnel will verify that study procedures are properly followed and that site personnel are trained and able to conduct the protocol appropriately. If the node personnel's review of study documentation indicates that additional training of site study personnel is needed, node QA personnel will undertake or arrange for that training. Details of the contract, node QA and data monitoring are found in the study QA monitoring plan.

14.8 Inclusion of Women and Minorities

All patients aged 18-75, inclusive, who have a diagnosis of OUD or are determined by the OUD-CDS algorithms to be at high risk for OUD and who meet all other protocol-defined eligibility criteria will be included in the study, regardless of sex or racial/ethnic group. Patients who have opted out of research will be excluded from analyses. All PCPs in randomized clinics will be included in the study, regardless of sex or racial/ethnic group. Patients who meet the per 45 CFR 46 Subpart C definition of prisoner will be excluded from surveys and interviews.

14.9 Prisoner Certification

As per 45 CFR 46 Subpart C, there are additional protections pertaining to prisoners as study participants. A prisoner is defined as any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Due to the nature of the OUD CDS, a prisoner certificate is not applicable to this data collection. Patient participants who meet the OHRP definition of "prisoner" will be ineligible for participation in any interview or survey.

14.10 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked at each participating site for regulatory document compliance prior to study initiation, throughout the study, as well as at study closure.

14.11 Records Retention and Requirements

Research records for all study participants will be maintained by the study team in a secure location for a minimum of 3 years after the study is completed and closed. These records are also

to be maintained in compliance with IRB, state and federal requirements, whichever is longest. The sponsor and Co-Lead Investigators must be notified in writing and acknowledgment from these parties must be received by the site prior to the destruction or relocation of research records.

14.12 Reporting to Sponsor

The lead investigators agree to submit accurate, complete, legible and timely reports to the Sponsor, as required. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the trial or increase risk to study participants. Safety reporting will occur as previously described. At the completion of the trial, the Co-Lead Investigators will provide a final report to the Sponsor.

14.13 Audits

The Sponsor has an obligation to ensure that this trial is conducted according to good clinical research practice guidelines and may perform quality assurance audits for protocol compliance. The Lead Investigator and authorized staff from the Northstar Node; the NIDA CTN (the study sponsor); NIDA's contracted agents, monitors or auditors; and other agencies such as the HHS, the OHRP and the IRB of record may inspect research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety.

14.14 Study Documentation

Each participating site will maintain appropriate study documentation (including medical and research records) for this trial, in compliance with ICH E6 R2 and regulatory and institutional requirements for the protection of confidentiality of participants. Study documentation includes all CRFs, workbooks, source documents, monitoring logs, sponsor-investigator correspondence, and signed protocol and amendments, ERC or IRB correspondence and approved consent form and signed participant consent forms. As part of participating in a NIDA-sponsored study, each site will permit authorized representatives from NIDA and regulatory agencies to examine (and when permitted by law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

14.15 Protocol Deviations

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

Any departure from procedures and requirements outlined in the protocol will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Sites will be responsible for developing corrective action plans for both major and minor deviations as appropriate. Those corrective action plans may be reviewed/approved by the Lead Node and the CCC with overall approval by the IRB of record. All protocol deviations will be monitored at each site for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial.

All protocol deviations will be recorded.

Additionally, each site is responsible for reviewing the IRB of record's definition of a protocol deviation or violation and understanding which events need to be reported. Sites must recognize that the CTN and IRB definition of a reportable event may differ and act accordingly in following all reporting requirements for both entities.

14.16 Safety Monitoring

14.16.1 Data and Safety Monitoring Board (DSMB)

An independent CTN DSMB will examine accumulating data to assure protection of participants' safety while the study's scientific goals are being met. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will provide an opinion on whether there is support for continuation of the trial, or evidence that study procedures should be changed, or if the trial should be halted, for reasons relating to the safety of the study participants, the efficacy of the treatment under study, or inadequate trial performance (e.g., poor recruitment).

14.16.2 Safety Events

This study is being conducted at the provider level using CDS prompts for evidence-based best practice standards related to OUD. As such, we are not trying to change the standard of care for OUD in primary care, but rather to help PCPs achieve this standard of care in their care of patients with OUD. Prior to implementation, we will train all intervention PCPs and their rooming staff on the importance of helping us identify any safety events or near-misses that may be related to the EHR or CDS. We will systematically educate them in identification of potential safety events and near-misses and informing us of these events via use of the Feedback Tab in the CDS or email. We will also ask PCPs to notify us of any clinical situations where their clinical judgment differs from the CDS. Use of the Feedback Tab automatically generates an email that is sent to the study team. The study team then discusses this feedback and any necessary actions, and connects with the PCP to answer the question, discuss steps taken to address the issue, or gather additional information and further trouble-shoot. In addition, at HealthPartners, the emails of Drs. Rossom and Sperl-Hillen are listed on the CDS interface for providers, and PCPs are encouraged to contact us directly with any questions or concerns if they'd rather not use the Feedback Tab in

the OUD-CDS. At Sites 2 and 3, study teams will determine what email address should be listed on the CDS interfaces for PCPs to contact with questions or concerns. All PCP feedback will be provided to the DSMB twice per year.

This is a minimal risk study. Adverse events and Serious Adverse events are not collected in the context of this trial. ED Visits, hospitalizations, Overdose events and deaths (all cause) will be captured through data pulls.

The site will follow local standard operating procedures (SOPs) for managing any medical or psychiatric emergencies.

15.0 DATA MANAGEMENT

15.1 Design and Development

The OUD-CDS itself will house the algorithms, communicate with and display within the EHR, and store data required to assess study objectives in a secure analytic database at HealthPartners Institute. These data, supplemented by EPIC Clarity data, will be used to assess CDS use rates, diagnosis of OUD, treatment of and referral for treatment of OUD, hospitalizations and emergency department visits. Data collected from the PCPs, patients and leadership via surveys will be collected and housed by the Data and Statistics Center.

15.2 Site Responsibilities

Investigators at each site, including a clinical champion at each site, will be responsible for leading healthcare system engagement with clinic and administrative leaders, and for partnering with Emmes to facilitate survey administration. An EPIC programmer at each site will be responsible for helping coordinate the installation of custom EPIC code to allow the OUD-CDS to run at the site. A data programmer at each site will be responsible for pulling preliminary Clarity data at each site to allow for harmonization of medication, lab, diagnosis and other data between each site and HealthPartners. In partnership with each site's study team, we will determine whether qualitative work at that site will be done by a site co-investigator or by the HealthPartners' team. Encounter data will be collected by the OUD-CDS itself from each care system, and each care system's data will be maintained separately on secure servers. The data programmer at each partner site will pull Clarity data to assess such outcomes as orders placed outside of the OUD-CDS tool, emergency department visits and hospitalizations.

15.3 Data Collection/Acquisition and Entry

Much of the data for this study will be collected directly by the OUD-CDS tool and stored on secure servers at HealthPartners behind multiple firewalls accessible only by authorized personnel. Programmers at each partner site will pull data from Clarity to assess such outcomes as orders placed outside of the OUD-CDS tool, ED visits and hospitalizations to send to HealthPartners, where these data will be stored on secure servers behind multiple firewalls and only accessible by authorized personnel.

15.3.1 Qualitative Data

All qualitative data will be collected and stored by each study site, with master files of all qualitative data stored at the main site. Original audio files will be kept on-site behind secure firewalls until transcription is complete. Verbatim transcripts of audio-recorded interviews will be made and de-identified before being stored on local, secure servers. All sites will collaborate on analysis of original, de-identified transcript data. Transcripts will be stored on secure servers behind multiple firewalls at each site. All field notes and other observation data will be kept by each site. Sites will contribute non-primary field note data to the study-wide implementation log described above, kept by HealthPartners. All qualitative data will be stored in a de-identified format until study completion. All identifiable qualitative data (audio recordings, speaker IDs) will be destroyed when analysis is complete.

15.3.2 Survey Data

All survey data will be collected and stored electronically by the DSC. The DSC will provide cleaned survey data back to the prime site for analysis. The link between the surveys and person identifiers will be maintained by the study teams. All necessary data agreements will be in place prior to exchange of identifiable data, and all parties will protect data behind secure firewalls according to institutional policies and IRB requirements.

16.0 PUBLIC ACCESS AND DATA SHARING PLAN

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN. Considerations for ensuring confidentiality of any shared data are described in **Section 14.5.**

Additional information is included in the CTN-0095 Data Share Plan.

17.0 PROTOCOL SIGNATURE PAGE

SPONSOR'S REPRESENTATIVE (CCTN SCIENTIFIC OFFICER OR DESIGNEE)

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 4.0 of the protocol and agree to conduct this clinical study in accordance with the design and provisions specified therein.
- I agree to follow the protocol as written except in cases where necessary to protect the safety, rights, or welfare of a participant, an alteration is required, and the sponsor and IRB have been notified prior to the action.
- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.
- I agree to personally conduct or supervise this investigation at this site and to ensure that all site staff assisting in the conduct of this study are adequately and appropriately trained to implement this version of the protocol and that they are qualified to meet the responsibilities to which they have been assigned.
- I agree to comply with all the applicable federal, state, and local regulations regarding the obligations of clinical investigators as required by the Department of Health and Human Services (HHS), the state, and the IRB.

SITE'S PRINCIPAL INVESTIGATOR

Printed Name	Signature	Date

Clinical Site Name _____

Node Affiliation _____

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19.0 APPENDIX A: DATA AND SAFETY MONITORING PLAN

Data and Safety Monitoring Plan Template

1.0 BRIEF STUDY OVERVIEW

Through CTN-0076-Ot, our team has developed and piloted a web-based and EHR-integrated Opioid Use Disorder (OUD) Clinical Decision Support (CDS) system to offer expert guidance to primary care providers (PCPs) on the management of OUD. The OUD-CDS has been implemented within the EPIC electronic health record (EHR) of one large care system and was piloted with 55 providers to ensure content validity and provider satisfaction. Our team will now implement this OUD-CDS in a large multi-site clinic-randomized controlled trial to evaluate its impact on practice process measures and patient outcomes. We also aim to prepare for scalability by evaluating facilitators and barriers to implementation, determining the costs of implementation and maintenance, and assessing cost effectiveness of the OUD-CDS. This study will randomize a minimum of 30 clinics to receive the OUD-CDS intervention or usual care (UC) across three large diverse healthcare systems. In intervention clinics, the OUD-CDS will identify patients at high risk for OUD, display the OUD-CDS and store analytic data from all eligible visits. In UC clinics, the OUD-CDS will run invisibly in the background to identify high risk patients and store analytic data.

2.0 OVERSIGHT OF CLINICAL RESPONSIBILITIES

A. Site Principal Investigator

Each participating site's Principal Investigator (PI) is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified, trained research staff and by overseeing training of PCPs to ensure adequate reporting of safety events as defined by the study protocol.

B. CCC Medical Monitor

It is not anticipated that a CCC Medical Monitor will be assigned to this study. Drs. Rossom and Sperl-Hillen and the Site PIs for Sites 2 and 3 will monitor all PCP feedback and make adjustments to the OUD-CDS as clinically indicated.

C. Data and Safety Monitoring Board (DSMB)

An independent CTN DSMB will monitor this study. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will provide an opinion on whether there is support for continuation of the trial, or evidence that study procedures should be changed, or if the trial should be halted, for reasons relating to the safety of the study participants, the effectiveness of the intervention under study, or inadequate trial performance (e.g., poor recruitment).

Following each DSMB meeting, the NIDA CCTN will communicate the outcomes of the meeting, based on DSMB recommendations, in writing to the study Lead Investigator. This communication summarizing study safety information will be submitted to participating IRBs.

D. Quality Assurance (QA) Monitoring

Quality assurance monitoring will be accomplished via pre-implementation testing to confirm that the CDS is collecting and storing the data as expected. After implementation and throughout the intervention phase, data will be repeatedly tested to ensure all data elements necessary for analysis are collected from all three sites on secure servers, and Dr. Crain will conduct periodic test analyses to ensure that all the data she requires for analysis are complete. Additionally, Drs. Rossom and Sperl-Hillen and investigators from Sites 2 and 3 will conduct periodic chart audits to ensure that data collected by the CDS is accurate and complete.

E. Management of Risks to Participants

Confidentiality

Confidentiality of participant records will be secured by the secure storage of any documents that have participant identifiers on-site, as well as secure computing procedures for collecting, storing, entering and transferring electronic data. Any documents or logs linking study codes with study participants on-site will be kept locked/secured separately from the study files and the medical records. No identifying information will be disclosed in reports, publications or presentations.

Information That Meets Reporting Requirements

We anticipate that the IRB of record will grant a waiver of consent for PCPs and patients to participate in the OUD-CDS intervention. PCPs will be using the OUD-CDS during their care of patients, and PCPs are required to report any suspected or known sexual or physical abuse of a child or elders to the appropriate authorities. PCPs are also expected to act on patient threats of violence to self and/or others.

Participant Protection

PCP participant protection: This study will provide OUD-CDS to approximately half of randomized primary care clinics and their employed PCPs. Practice decisions made during the course of any patient encounters will not be reported to the practice group, thus preventing adverse employment or incentive-based decisions being made solely as a result of study participation.

Patient participant protection: With this work, we are not attempting to change the standard of care for OUD treatment in primary care, but rather are attempting to help PCPs achieve this standard of care in OUD treatment. There is a small but important risk that the OUD-CDS may malfunction or provide inaccurate information. PCPs will be trained that, as with other clinical decision tools, the OUD-CDS is meant to supplement but not supersede clinical judgment. PCPs can choose to follow or not follow the guidance of the CDS at any given time for any given patient. PCPs will be asked to use the Feedback Tab within the tool to let the team know of questions or potential errors in the CDS. Additionally, PCPs are trained to let the research team know via the Feedback Tab when their clinical judgment is inconsistent with the CDS. This feedback will be monitored by the treatment team and the CDS algorithms adjusted if indicated.

Pregnancy

There are algorithms specific to treatment of pregnant women in the OUD-CDS. At HealthPartners clinics, for example, it is recommended that all pregnant women at high risk for OUD be referred to the Healthy Beginnings program for treatment by high-risk perinatologists and consideration of treatment with monotherapy buprenorphine for OUD. There are also algorithms that recommend

pregnancy tests for women of child-bearing ages throughout the OUD-CDS. Algorithms guiding the referral of pregnant women with OUD to specialty care is anticipated to be different at each study site, but the algorithms will be consistent in informing PCPs that pregnant women with OUD require referral to specialty care.

Study Specific Risks

There is a small but important risk that the OUD-CDS could provide the wrong treatment advice at the wrong time. As with other clinical decision tools, the Opioid Wizard makes suggestions for patient care that are meant to supplement but not supersede clinical judgment. PCPs can choose to follow or not follow the guidance of the CDS at any given time in any given patient encounter. PCPs will be trained to let the research team know via the Feedback Tab in the CDS when their clinical judgment leads them to a different action than that suggested by the CDS. These events will be monitored by the treatment team and the CDS algorithms adjusted if there are found to be errors. Every clinical encounter requires medical judgment and poses some element of risk to patients. In the situation of a PCP who is unfamiliar or uncomfortable with OUD, use of the CDS will likely make care safer by providing suggestions to screen and assess for OUD using validated tools, and to encourage referrals when patients are classified as high risk. We will not be encouraging buprenorphine use in non-certified providers, and this will be reinforced thoroughly in provider training on the CDS. For buprenorphine-certified providers, the use of the CDS may improve the likelihood of using Medication Assisted Treatment (MAT) in high risk situations; however, the risks of MAT are generally considered lower than untreated OUD in high-risk situations.

3.0 DATA MANAGEMENT PROCEDURES

This protocol will utilize a centralized Data and Statistics Center (DSC). A web-based distributed data entry model will be implemented. This electronic data capture system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems in clinical trials are upheld. Data collected by the OUD-CDS and from Clarity pulls will be stored on secure servers behind multiple firewalls at HealthPartners Institute in a secure project folder only accessible by authorized study personnel.

4.0 DATA AND STATISTICS CENTER RESPONSIBILITIES

The DSC will: 1) develop and apply data management procedures to ensure the collection of accurate and good-quality survey data, 2) prepare instructions for the use of the electronic data capture system, 3) conduct ongoing monitoring activities on study data collected from all participating sites, and 4) perform survey data cleaning activities as necessary prior to the transfer of data resulting from the conduct of each survey. There will be no interim monitoring analyses for this study.

5.0 DATA MONITORING, CLEANING AND EDITING

All OUD-CDS, Clarity and interview data will be monitored, cleaned and edited at HealthPartners Institute on secure servers and accessible only by study personnel. Survey data will be monitored, cleaned and edited by the DSC.

6.0 DATABASE LOCK AND TRANSFER

At the conclusion of data collection for each survey, the DSC will perform final data cleaning activities and will “lock” the survey database from further modification. The final analysis dataset will be transferred to the Lead Investigator or designee. De-identified versions of these datasets will also be provided to the NIDA CCTN-designated parties for posting on Datashare, as well as storage and archiving.

Reference: http://grants.nih.gov/grants/guide/notice-files/not98-084.html