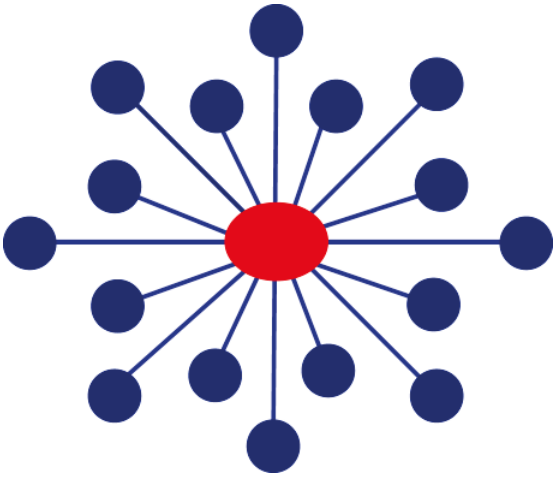

NIDA CTN Protocol 0076-ot

Clinical Decision Support for Opioid Use Disorders in Medical Settings: Pilot Usability Testing in an EMR (COMPUTE)

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
CDS	Clinical decision support
CTN	Clinical trials network
DEA	Drug Enforcement Agency
DSMB	Data Safety Monitoring Board
EMR	Electronic medical record
HPMG	HealthPartners Medical Group
MAT	Medication-assisted therapy
MD	Medical doctor
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NP	Nurse practitioner
OUD	Opioid use disorder
PA	Physician assistant
PCP	Primary care provider
PNMG	Park Nicollet Medical Group

2.0 STUDY SYNOPSIS

2.1 Study Objectives

The primary objective of this pilot study is to program an opioid use disorder (OUD) clinical decision support (CDS) tool for use in an electronic medical record (EMR) and obtain high primary care physician (PCP) usability and acceptability. The OUD-CDS is based on the NIDA-Blending Initiative white paper, “Clinical Decision Support for Opioid Use Disorders: Working Group Report,” which itself is based on national evidence-based guidelines (American Society of Addiction Medicine (ASAM 2015), VA (VA 2015). As such, this pilot study aims to help PCPs achieve accepted standards of care in OUD treatment. The secondary objectives of this pilot study are to evaluate the usefulness of the tool by comparing OUD case-finding, medication-assisted therapy (MAT) and referral patterns pre- and post-CDS deployment for PCPs with and without CDS access.

2.2 Study Design and Outcomes

This pilot study will test the usability and acceptability of a CDS tool for OUD in primary care clinics. Details of each phase are found in Section 10.0. Phase 1 of the study involves translating the Blending Initiative White Paper into algorithms that are compatible with Epic and HPMG and PNMG workflows and then building and extensively testing the CDS. Phase 1 lasts 15 months. Phase 2 of the study involves deploying and testing the usability of the CDS in primary care. We will recruit 16 non-waivered PCPs from multiple clinics to receive access to the OUD-CDS (8 MDs and 8 nurse practitioners (NPs) or physician assistants (PAs)), as well as 16 non-waivered PCPs from multiple clinics who will not receive access to the OUD-CDS (8 MDs and 8 NPs/PAs).

Additionally, all 11 waivered PCPs (10 MDs, 1 NP) will be invited to participate and will receive access to the OUD-CDS. All PCPs will complete baseline and 6-month surveys; PCPs with access to the OUD-CDS will also be asked and incentivized to submit feedback about the CDS via the feedback tab in the CDS. A recruitment diagram can be found in Section 7.3. Phase 2 lasts 6 months. Phase 3 involves analysis and reporting of data and lasts 3 months.

The study outcomes are delineated in the specific aims in Sections 5.0 and 9.0.

2.3 Sample Size and Study Population

This pilot study will include 16 non-waivered volunteer PCPs from multiple HPMG and PNMG primary care clinics in the HealthPartners integrated healthcare organization who will receive access to the OUD-CDS. This pilot study will also include 16 non-waivered volunteer PCPs who will not receive access to the OUD-CDS but, similar to intervention PCPs, will complete baseline and 6-month surveys. Additionally, all 11 PCPs waivered to prescribe buprenorphine will be invited to participate in this pilot.

2.4 Treatment/Assessment/Intervention and Duration

The intervention involves access to the OUD-CDS for approximately half of recruited PCPs. Survey-based assessment of confidence in OUD screening, assessment, treatment and referral will be compared before and after the 6-month pilot for PCPs with and without CDS access.

Metrics of OUD-CDS use will be monitored for each PCP with CDS access throughout the 6-month intervention period. Specifically, we will monitor rates of OUD-CDS use for eligible encounters (i.e., PCP with CDS access who has an encounter with a patient with OUD or with a patient identified by the OUD-CDS to be at high risk of OUD).

2.5 Safety Reporting

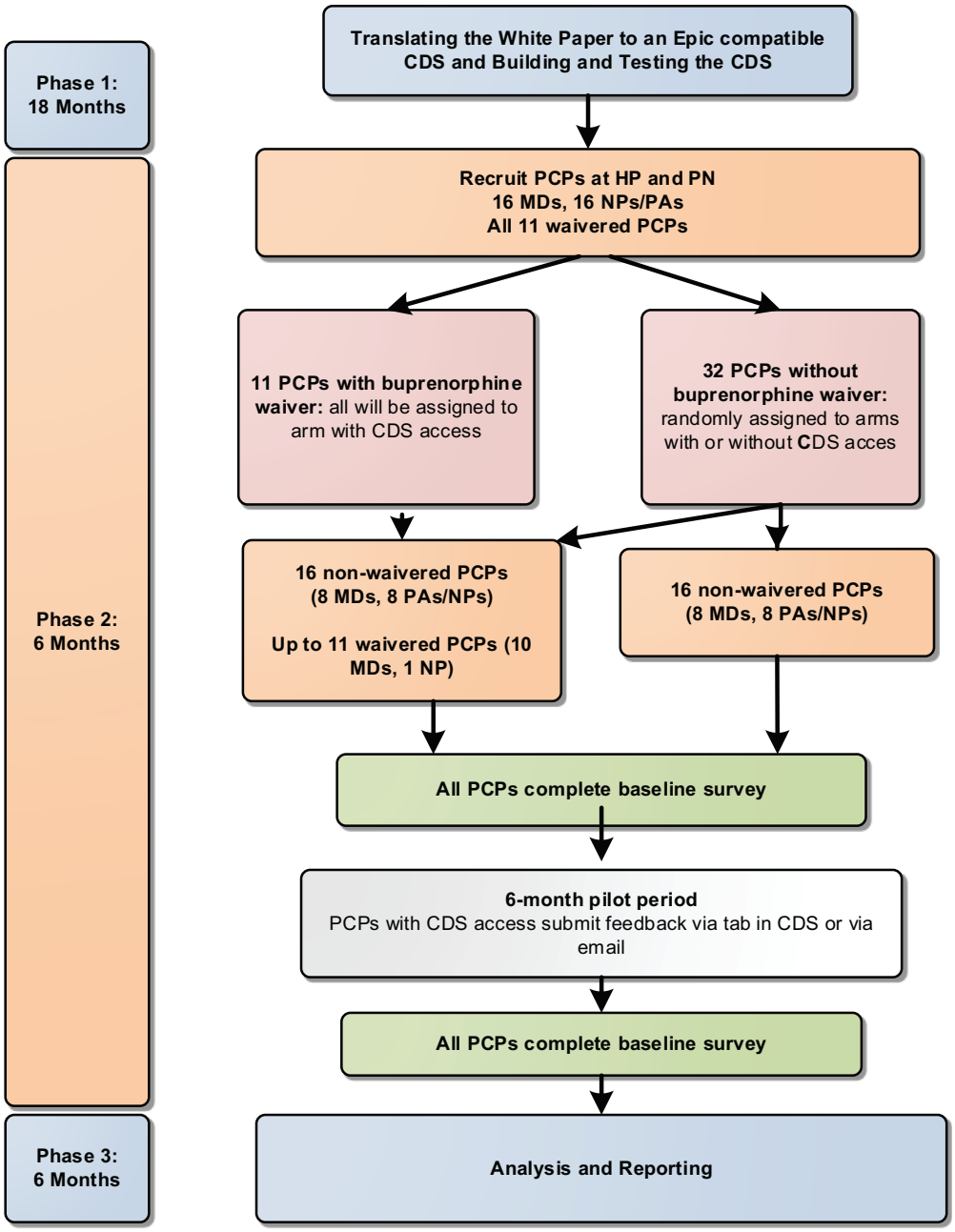
In this pilot study, we are not trying to change the standard of care for OUD treatment in primary care, but rather we are helping PCPs achieve this standard of care in OUD treatment. PCPs are trained that, as with other clinical decision tools, the OUD-CDS is meant to supplement but not supersede clinical judgment. PCPs can choose to follow or not follow the guidance of the CDS at any given time for any given patient, and PCPs are trained to let the research team know via the Feedback tab in the CDS 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 CTN DSMB will monitor this study. The DSMB will communicate regarding what type of reports will be needed, as well as frequency. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine 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).

2.6 Analyses

This pilot study for OUD-CDS feasibility and usability will not have a statistical endpoint. Provider characteristics and OUD-CDS use data will be tracked and descriptively analyzed. Pre- and post-surveys of provider confidence in OUD screening, assessment, treatment and referral, as well as satisfaction with the OUD-CDS, will be described.

3.0 STUDY SCHEMA



4.0 INTRODUCTION

4.1 Background and Significance to the Field

We are in the midst of an epidemic of opioid misuse (Centers for Disease Control and Prevention 2012). Between 2007 and 2012, past-month heroin use increased 75% while past-month non-medical prescription opioid use remained relatively stable (Substance Abuse and Mental Health Services Administration 2008; Substance Abuse and Mental Health Services Administration 2014). In 2015 there were approximately 2.5 million Americans with moderate-to-severe OUD (Grant et al. 2016; Substance Abuse and Mental Health Services Administration 2014). Approximately 20% of these individuals entered into addiction treatment programs but, of these, only about 25% received MAT (Substance Abuse and Mental Health Services Administration 2012). Overall, less than 10% of these 2.5 million Americans received treatment in a doctor's office (Substance Abuse and Mental Health Services Administration 2014).

Because primary care is the most common point of healthcare contact in the United States, identification and treatment of OUD in primary care may help reduce this significant treatment gap. While methadone is highly regulated, of limited geographic availability, and allowed only in licensed treatment programs, buprenorphine is a cost effective treatment for OUD that can be deployed in specialty and primary care settings (Alford et al. 2011; Liebschutz et al. 2014; Moore et al. 2007; Schackman et al. 2012; Soeffing et al. 2009; Weiss et al. 2011) and monthly injections of extended-release naltrexone (XR-NTX) are showing promise for OUD in some general medical settings (Coviello et al. 2012). Further, treating OUD in primary care may facilitate the diagnosis and treatment of unrecognized chronic medical conditions (Rowe et al. 2012).

Since its introduction in 2003, more than 35,000 physicians have been licensed to prescribe buprenorphine for the treatment of OUD. Under current law, 23,982 of these can prescribe for up to 30 patients, 9,285 for up to 100 patients, and 2,525 for up to 275 patients (http://www.samhsa.gov/programs-campaigns/medication-assisted-treatment/physician-program-data, accessed November 28, 2016). Fewer than 30% of trained physicians go on to prescribe buprenorphine and less than 60% of the overall buprenorphine treatment capacity is filled (Arfken et al. 2010; Hutchinson et al. 2014; Kunins et al. 2012). It is too soon to know if the recent addition of advance practice clinicians to those eligible to prescribe will impact access or capacity. Whatever the case, at least for physicians, there is an additional barrier beyond certification and training that is preventing the uptake of buprenorphine prescription. Compared to those who do prescribe buprenorphine, those who do not are more likely to endorse lack of institutional support as being a barrier. Other barriers identified by both prescribers and non-prescribers include lack of staff training, lack of confidence, poor access to clinical guidelines, and time constraints (Barry et al. 2009; Hutchinson et al. 2014; Netherland et al. 2009; Walley et al. 2008). Similar barriers have been identified as limiting use of XR-NTX (Alanis-Hirsch et al. 2016).

The various iterations of the Physician Clinical Support System (PCSS) have attempted to provide free education and mentoring support to assist providers in using MAT for OUD (Egan et al. 2010). This assistance is available as web-based documents, webinars, telementoring, and even as site visits arranged between mentors and providers. Unfortunately, these valuable services are rarely deployed or utilized during actual patient encounters.

In the last decade, EMR-linked web-based point-of-care CDS systems designed to improve quality of chronic disease care have become increasingly sophisticated and successful (Ammenwerth et al. 2012; Druss & Dimitropoulos 2013; Roshanov et al. 2012). Our team has developed CDS systems that have been shown to improve glucose and blood pressure control in adults with diabetes, increase recognition of adolescents with previously unrecognized hypertension, have 60-80% use rates at targeted primary care clinical encounters, and have 95% primary care provider satisfaction ratings (Desai et al. 2013; Gilmer et al. 2012; Kharbanda et al. 2015; O'Connor et al. 2009; O'Connor et al. 2011; Sperl-Hillen et al. 2010). These CDS systems, which focus on cardiovascular risk factor identification and management, have been used daily for the past 3-4 years in the care of 1.5 million patients in 3 large healthcare delivery systems and will soon be deployed to an additional large healthcare system. NIH funding has been secured to expand this CDS system to include identification and management of additional chronic conditions. It is now technically feasible to extend this technology to support the systematic, timely, and safe management of those with OUD in primary care and other settings.

Currently, providers lack real-time CDS tools that can efficiently facilitate personalized identification, assessment, and treatment of patients with OUD prior to or during a clinical encounter. The NIDA CTN Blending Initiative has developed an expert panel framework for an OUD-CDS. The framework has been previewed by PCPs at the 2015 International Network on Brief Interventions for Alcohol and Other Drugs (INEBRIA) conference. It is felt that any further refinements needed are best identified through piloting so that provider acceptance and feasibility of use, including workflow issues, can be addressed.

5.0 OBJECTIVES

5.1 Primary Objectives

1) To program an OUD-CDS tool based on a NIDA-Blending Initiative white paper “Clinical Decision Support for Opioid Use Disorders: Working Group Report” and national guidelines (VA (VA 2015), ASAM (ASAM 2015)) for use in an EMR.

   Measure 1. Demonstrate that the OUD-CDS is functional and accurate through:
   a) Testing in the EMR test environment,
   b) Chart audit validation of CDS output, and
   c) Approval of the tool by specialty addiction physician and PCP pilot testers prior to the full rollout.

2) To descriptively analyze PCP acceptability, satisfaction and use rates high enough to demonstrate proof of concept

   Measure 2A. By the end of the 6-month pilot intervention, the monthly PCP use rate of the CDS for targeted high-risk patient encounters for PCPs with CDS access will be >60%.

   Measure 2B. By the end of the 6-month pilot intervention, >60% of PCPs with CDS access will report feeling confident in assessing and treating OUD

Measure 2C. At the end of the 6-month pilot intervention, >80% of PCPs with CDS access will rate the OUD-CDS ≥4 on a 5-point Likert scale of likeliness to recommend use of the tool to their colleagues.

5.2 Secondary Objective(s)

We will examine the usefulness of the OUD-CDS tool by comparing pre- and post-intervention rates of screening for OUD in high-risk patients, Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) use, OUD diagnosis, use of medication-assisted therapy, as well as treatment referral patterns, for 3 groups of PCPs: (1) those with CDS access and buprenorphine certification, (2) PCPs with CDS access but without buprenorphine certification, and (3) PCPs without CDS access.

Where possible, we will structure these secondary outcome measures to be similar to nationally-used clinical quality measures, such as:

a) Initiation of pharmacotherapy upon new episode of OUD (Number of patients who receive at least 1 prescription for MAT within 30 days following index visit with a diagnosis of OUD, divided by the number of patients with index visit associated with an OUD diagnosis after 60-day clean period without OUD documentation)(Washington Circle Group; DHHS 2015)

b) Maintenance pharmacotherapy for OUD (patients who receive at least 30 days' treatment with buprenorphine or naltrexone for OUD, divided by patients who receive a diagnosis of OUD during the 6-month pilot phase)(American Psychiatric Association; DHHS 2015)

6.0 STUDY DESIGN

6.1 Overview of Study Design

This 24-month pilot study will primarily entail programming the OUD-CDS into an EMR environment. This will be an iterative process with input from addiction specialists and PCPs to make sure bugs that may arise during clinical implementation are identified and corrected. We anticipate that programming the CDS into the EMR will take 12 months to complete.

Upon completion of the programming phase, the OUD-CDS will be tested in multiple ways: 1) We will test the algorithms using real patient data in the EMR testing environment, 2) We will run the algorithms in the background of the production EMR environment without PCP displays, testing primarily data capture and operability, 3) We will pilot the OUD-CDS with one or more providers with extensive experience in OUD care.

Once live EMR assessment has been completed and any programming adjustments made, the OUD-CDS will be deployed for all PCPs with CDS access at PNMG and HPMG. Confidence in assessing and treating OUD prior to and 6-months following the go-live date will be assessed via survey for all PCPs with and without CDS access. PCPs with CDS access will also be surveyed about the usefulness and ease of use of the CDS at 6-months.

6.2 Duration of Study and Visit Schedule

PCPs with CDS access will use the OUD-CDS for 6 months. During the 6-month intervention phase, data on use patterns of the OUD-CDS will automatically be collected for both PCPs with CDS access and PCPs without access by the OUD-CDS. For PCPs without access, the OUD-CDS will run behind the scenes, without displaying, to collect these data. In this way, patterns of OUD-related care can be compared on similar patients presenting to PCPs with and without CDS access to quantify the impact of the OUD-CDS on OUD identification and care. Automatic identification of eligible patients is done by the OUD-CDS algorithms, independent of any PCP actions.

7.0 STUDY POPULATION

We will recruit 16 non-waivered PCPs from multiple clinics to receive access to the OUD-CDS (8 MDs and 8 nurse practitioners (NPs) or physician assistants (PAs)), as well as 16 PCPs from multiple clinics who will not receive access to the OUD-CDS (8 MDs and 8 NPs/PAs). Additionally, all 11 waivered PCPs (10 MDs, 1 NP) will be invited to participate and will receive access to the OUD-CDS. All PCPs will complete baseline and 6-month surveys; PCPs with access to the OUD-CDS will also be asked and incentivized to submit feedback about the CDS via the feedback tab in the CDS. Including multiple PCPs across multiple clinics, including both MDs as well as PAs and NPs, will provide a better understanding of the feasibility and usefulness of the OUD-CDS across different providers, locations and patient populations.

7.1 Participant Inclusion Criteria

Eligible clinicians will:

a) Be an MD, Doctor of Osteopathy, Nurse Practitioner or Physician's Assistant engaged in independent primary care of adults
b) Have at least schedule 3 DEA prescribing privileges
c) Voluntarily provide written informed consent to participate in this study

7.2 Participant Exclusion Criteria

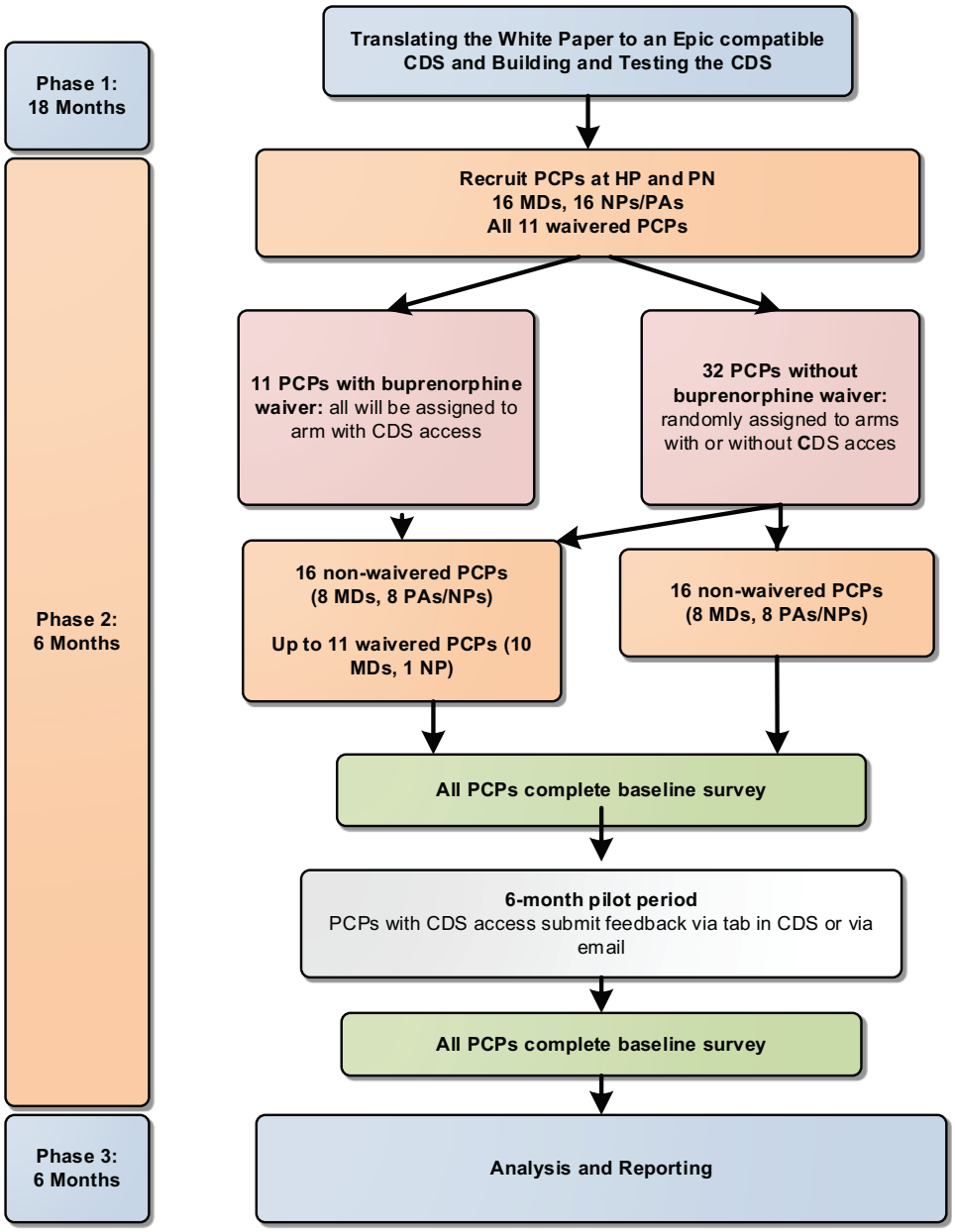
Less than half-time clinical primary care responsibilities

7.3 Participant Recruitment

PCPs will be voluntarily recruited from HPMG and PNMG in person and via emailed invitations and other IRB-sanctioned methods. We will preferentially recruit those PCPs who have or will soon have buprenorphine waivers, as they will be able to use the entirety of the OUD-CDS tool. In our invitation to participate in the study, we will inform PCPs that they will receive $150 (PCPs without CDS access) to $300 (PCPs with CDS access) each to compensate them for their time to complete electronically administered surveys at the beginning and end of the 6-month pilot intervention phase (PCPs with or without CDS access) and submission of feedback via the feedback tab in the CDS itself (PCPs who have access to the CDS). Approximately half of recruited PCPs will receive access to the OUD-CDS; all PCPs with buprenorphine certification will be allotted to this group. Approximately half of recruited PCPs will not receive OUD-CDS

access. PCPs without buprenorphine certification will be randomized to receive or not receive access to the CDS.

Recruitment diagram:



8.0 SITE SELECTION

8.1 Number of Sites

We anticipate approximately twenty HPMG and PNMG primary care clinics will be represented by the PCPs enrolled in this trial..

8.2 Site Characteristics

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 HPMG and 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.

PCPs who practice at least half-time and who have at least schedule 3 DEA prescribing privileges at HPMG or PNMG will be invited to participate in this study. PCPs with buprenorphine prescribing waivers will be particularly encouraged to participate in the study.

8.3 Rationale for Site Selection

Rather than restricting the intervention to a single primary care clinic, particularly given the low prevalence of buprenorphine-certified PCPs in any one clinic, we propose inviting PCPs across HPMG and PNMG to participate. This approach will allow for maximum exposure of the OUD-CDS across different providers, locations and patient populations. Making this intervention voluntary ensures maximum support of primary care leadership at both Park Nicollet and HealthPartners, and the timing of our study is ideal, with 12 PCPs intending to become newly buprenorphine-certified in the first half of 2017 across HPMG and PNMG.

9.0 OUTCOME MEASURES

9.1 Primary Outcome Measure

Primary Aims:

1) To program an OUD-CDS tool based on a NIDA-Blending Initiative white paper “Clinical Decision Support for Opioid Use Disorders: Working Group Report” and national guidelines (VA (VA 2015), ASAM (ASAM 2015)) for use in an EMR.

   Measure 1. Demonstrate that the OUD-CDS is functional and accurate through:
   a) Testing in the EMR test environment,
   b) Chart audit validation of CDS output, and
   c) Approval of the tool by specialty addiction physician and PCP pilot testers prior to the full rollout.

2) To descriptively analyze PCP acceptability, satisfaction and use rates high enough to demonstrate proof of concept

Measure 2A. By the end of the 6-month pilot intervention, the monthly PCP use rate of the CDS for targeted high-risk patient encounters for PCPs with CDS access will be >60%.

Measure 2B. By the end of the 6-month pilot intervention, >60% of PCPs with CDS access will report feeling confident in assessing and treating OUD

Measure 2C. At the end of the 6-month pilot intervention, >80% of PCPs with CDS access will rate the OUD-CDS ≥4 on a 5-point Likert scale of likeliness to recommend use of the tool to their colleagues.

Secondary Aims. We will examine the usefulness of the OUD-CDS tool by comparing pre- and post-intervention rates of screening for OUD in high-risk patients, TAPS use, OUD diagnosis, use of medication-assisted therapy, as well as treatment referral patterns, for 3 groups of PCPs: (1) those with CDS access and buprenorphine certification, (2) PCPs with CDS access but without buprenorphine certification, and (3) PCPs without CDS access.

Where possible, we will structure these secondary outcome measures to be similar to nationally-used clinical quality measures, such as:

a) Initiation of pharmacotherapy upon new episode of OUD (Number of patients who receive at least 1 prescription for MAT within 30 days following index visit with a diagnosis of OUD, divided by the number of patients with index visit associated with an OUD diagnosis after 60-day clean period without OUD documentation)(Washington Circle Group; DHHS 2015)

b) Maintenance pharmacotherapy for OUD (patients who receive at least 30 days' treatment with buprenorphine or naltrexone for OUD, divided by patients who receive a diagnosis of OUD during the 6-month pilot phase)(American Psychiatric Association; DHHS 2015)

9.2 Other Outcome Measures

MAT has been shown to reduce adverse outcomes, such as overdoses, emergency room visits, hospitalizations and deaths, for patients with OUD (Mohlman 2016; WHO 2013; Cornish 2010; Lo-Ciganic 2016). As a quality measure to inform future implementation studies of this OUD-CDS, we will collect and report available EHR data on overdoses, ER visits, hospitalizations and deaths for patients identified by the CDS as being at high-risk for OUD or as having been diagnosed with and/or treated for OUD. This data will be collected for patients of both PCPs with and without CDS access; for PCPs without CDS access, the CDS will still be collecting data behind the scenes without any displays to the PCP.

10.0 STUDY PROCEDURES

10.1 Phase 1: Translating the White Paper to an Epic-compatible CDS and Building and Testing the CDS (15 months)

10.1.1 Project Initiation

1. The original Blending Initiative team that developed the OUD CDS white paper will serve as an advisory panel to this project.
2. The project team includes a co-chair of the Blending Initiative OUD CDS white paper team, Dr. Gavin Bart, a co-lead of this project, and a working group of clinicians and researchers with multidisciplinary expertise in OUD and EMR-based CDS, programmers experienced in web development, and programmers who are experienced in programming changes to the EMR.
3. The project team will meet frequently (on average weekly) throughout the duration of this project.

10.1.2 Design and Planning

4. The entire team needs to gain a deep understanding of the whitepaper. Since the CDS has to work in a real-world setting, we will collaborate with personnel who work in these settings and have knowledge-sharing meetings with them. Investigators and project managers will also visit clinics to perform work-site analyses and obtain advice and input from PCPs and clinic managers on how to integrate OUD-CDS within clinic workflows and strategies to optimize use rates. Once these data are collected, a plan is laid out that inserts CDS interactions at key points of the clinic workflow.
5. We will refine the OUD algorithm and trouble-shoot potential operational issues using Visio and other software. Each step in the algorithm requires decisions about multiple aspects of care, including definitions of conditions and medical comorbidities, exclusion criteria, identification of pertinent labs and medications, and appropriate look-back periods. The CDS algorithms will be simplified and will include decision trees that will direct PCPs towards a referral for specialty addiction treatment for complicated cases, such as if a patient has both OUD and at least one other substance use disorder or uncontrolled behavioral health conditions.
6. The CDS programs will then be designed to fit into the primary care clinic workflows. As envisioned currently: (a) When the rooming staff enter a blood pressure and close the vitals section in Epic, this triggers communication between Epic and the web server and the OUD CDS will run the algorithms. (b) For patients identified at high risk for OUD, a best practice advisory will display for the rooming staff to open and print the CDS. The rooming staff will give the CDS to the PCP prior to the office visit so that the PCP is aware that the patient is potentially at risk for OUD and requires screening, diagnosis and/or treatment. The PCP will then re-enter the CDS during the encounter. (c) We train both the PCP and rooming staff in these procedures and the importance of this workflow. (d) Use rates are monitored by the research team with active outreach to clinics and providers who have lower than expected CDS use rates. (e) We will survey PCPs about the support staff and services they currently have in place and what kinds of support or staff they would like to see in place to further inform our study and implementation.
7. We will program OUD clinical algorithms in a web-based platform and ensure secure and timely communication between the web-based platform and HealthPartners' EpiCare EMR

(Epic; Verona, WI). Steps 5 and 6 are time-consuming and require multiple iterative tests to optimize the process and assure data validity.

8. While the CDS will always be available to be manually triggered by PCPs for any patient encounter, we will also set thresholds for the CDS to present a prompt or reminder for PCPs to suggest use of the CDS for screening patients identified at high risk for OUD. We will identify the criteria for automatic deployment in an iterative process, informed by preliminary data of the prevalence of comorbid diagnoses from our EMR and a recent big data study on the risk of OUD in patients receiving an initial opioid prescription (Cochran 2014). We anticipate a waterfall approach that may, for example, identify patients with (1) one inpatient or two outpatient diagnoses of OUD in the past 2 years, (2) 4 or more prescriptions for opioids in the past 2 years, and (3) diagnoses of non-opioid drug or alcohol use disorders, including sedative/hypnotics, cocaine, or cannabis. The process to trigger the CDS will be modified based on feedback we receive from PCPs in the pilot so as not to be overly burdensome to their workflow. PCPs will be encouraged to open the CDS for patients identified by the CDS to be at elevated risk for OUD and screen such patients using the sections of the Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) tool specific to OUD (McNeely 2016) that will be programmed as a smartform within Epic.
9. The programs have many layers of abstraction achieved by each layer performing a specific task. The layer above it can work in generalizations without specific knowledge of the tasks performed in the previous layer. The top layer of this stack will run the high-level decisions involved in the CDS. Design decisions are also based on what type of information is needed and where and when it is available for extraction from the EMR. In certain cases, the data required are not in the EMR and we will have to make alternate plans to collect such data from the patient and/or provider.
10. We will design provider and patient print-outs for the OUD-CDS that PCPs can use as shared-decision-making tools with their patients. Traditionally, the provider print-out has had more details and specific treatment suggestions, while the patient version has included the same basic information without relying on high literacy or numeracy. However, we have found that some PCPs prefer to review the provider print-out with patients, and keep this in mind as we design these forms.

10.1.3 Development

11. Once the design of the system is in place, we will begin programming. We will use a Java Platform, with the components of the stack being Oracle databases hosted on AIX LAPR, a Tomcat web server that is hosted on Linux VM. The server infrastructure is designed for maximum uptime and is hosted in a secure offsite data center. The network is designed to handle data requested in a round robin fashion, thereby providing load balancing and failover capabilities. The CDS is implemented as a SOAP web service, which enables flexible maintenance and upgrade that is independent of the EMR.
12. Data storage and structures will be defined and used to store data for later analysis. The data model will be created in a modeling platform that will be shared with the database

administrators for approval. The necessary security measures will be put into place to ensure minimum necessary access to data. Provider interfaces will be designed and implemented based on best practices. Data exchange formats will be decided upon for exchange of data between the web service and EMR.

13. Our expert EMR programmers will create builds in the EMR to insert CDS into the workflow. They will also code the routines that extract patient data and package and format it for exchange. Additionally, they will configure and code hooks that will create and customize smartsets into the EMR that will help PCPs order the components suggested by the CDS. For patient reported data not already minable within the EMR, we will develop a section within a dynamic smartset tool to use for additional data collection.
14. Development and programming will be iterative processes with multiple cycles of development and testing until a product is finalized. Multiple rounds of chart audits will be conducted to identify problems in the algorithm or in data capture for use in the algorithms. Drs. Rossom and Sperl-Hillen will audit a minimum of 25 charts, increasing the sample by 10 charts each time we deem further review necessary, stopping when they agree they are no longer identifying additional issues to troubleshoot in the sample. Depending on what issues are identified in this iterative, ongoing process, the team may need to complete several series of chart audits to further test any changes in programming indicated by previous testing.

10.1.4 Testing

15. Once internal testing is performed and approvals are in place, the CDS will be turned on in the background for PCPs without any displays or visual indicators to the PCPs that the CDS is running. This allows us to test the CDS for data flow back and forth between the EMR and web platform and assess adequate capture of data in the web service.
16. Once this testing is complete, the CDS will then be tested for clinical use by one or more providers with extensive experience with OUD care in an Epic testing environment.
17. After this testing is completed by a provider with content expertise, we will conduct usability testing with at least three clinicians, observing them using the CDS in person in the production or testing environment. We will use a “talk or think aloud” protocol to identify any screen design or other usability issues.
18. During these testing phases, we will test output of the care algorithms in batch process. We continuously validate collected data and closely monitor usage, traffic and accuracy.
19. Infrastructure and data security will be maintained by having regular system-wide scans and by following documented standards and procedures to delegate access to data. Systems will be constantly monitored for errors.
20. We will modify the smartsets and active guidelines as needed to provide actionable order sets for medications, labs, and referrals, automatic population of patient instructions, and facilitation of diagnostic coding based on algorithmic suggestions.
21. We will develop reports to monitor usage at the provider level, provide feedback to PCPs and trouble-shoot low use rates.

22. We will recruit PCPs in-person and via emailed invitations approved by the IRB.
23. We will assign PCPs to receive or not receive OUD access.
24. We will assess confidence in assessing and treating OUD at baseline via an electronic survey for PCPs with and without CDS access

10.2 Phase 2: Deploying and Testing the CDS in Primary Care (6 months)

25. We will deploy OUD-CDS to approximately half of consented PCPs
26. We will obtain feedback on OUD-CDS from PCPs in real-time in association with patient encounters via the feedback tab in the CDS and update the algorithms when indicated by this feedback
27. We will measure and report use rates of the OUD-CDS at targeted visits by each PCP and trouble-shoot low use rates. For PCPs with use rates <60% of targeted visits, we will meet with the PCP to better understand why use rates are low, trouble-shoot any identified barriers, and encourage increased use.
28. We will update and troubleshoot the CDS algorithms as needed, based on internal monitoring, provider feedback, FDA changes in treatment indications, or changes in the clinical evidence base or guideline recommendations.

10.3 Phase 3: Analysis and Reporting (3 months)

29. After the 6-month pilot phase, we will reassess provider confidence in assessing and treating OUD for PCPs with and without CDS access, and obtain feedback on OUD-CDS usability and satisfaction from PCPs with CDS access, via electronic survey
30. Data will be consolidated, cleaned and analyzed
31. We will disseminate findings locally and nationally, and submit manuscripts for publication

10.4 Informed Consent Procedures for Participants

We are asking PCPs to give informed consent to use the OUD-CDS on a voluntary and optional basis (if in the group of PCPs who are assigned to receive CDS access) and complete the pre- and post-intervention surveys. As the OUD-CDS is essentially operationalizing national and regional clinical guidelines, we will not be consenting PCPs to specifically change any clinical behavior related to managing patients with OUD. 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 CDS makes suggestions for patient care and is meant to supplement but not supersede the PCP's clinical judgment. This point is made clear in the training, in the consent, and on the provider display for the CDS. We will seek an IRB waiver of written informed consent for primary care clinic patients, as the CDS does not recommend any new care procedures and is being applied within the EMR as an aid to the PCP to facilitate recommended standards of care. HealthPartners IRB has granted waivers for other studies of CDS in the past.

10.5 HIPAA Authorization and Medical Record Release Forms

Not applicable.

10.6 Baseline Visit

Not applicable.

10.7 Randomization

PCPs who are recruited and are buprenorphine-certified will be placed into the group of PCPs who have OUD-CDS access. PCPs who are recruited and do not have buprenorphine certification will be randomized to receive or not receive access to the OUD-CDS.

10.8 Treatment/Intervention

The intervention is the availability of the OUD-CDS to approximately half of enrolled PCPs.

10.9 Collection of Biospecimens

Not applicable.

10.10 Premature Withdrawal of Participants

All consented PCPs will be followed for the duration of the study unless they withdraw consent, die, leave HPMG or PNMG or the investigator or sponsor decides to discontinue their enrollment for any reason. Reasons for the investigator or sponsor terminating a participant from the study may include, but are not limited to lack of funding or early termination of the study for safety or effectiveness reasons.

10.11 Study Halting Rules

While not anticipated, if it becomes clear that it is technically too difficult or otherwise unfeasible to program the CDS into a web-based platform that displays within the EMR, the study may be stopped early.

10.12 Follow-Up

We will collect follow-up survey information from PCPs 6 months after the OUD-CDS go-live date. During the 6-month intervention phase, we will be monitoring PCP use of the CDS, providing use rate reports for PCPs, and contacting PCPs whose use rates fall below 60% to trouble-shoot low use and understand any barriers to use.

10.13 Blinding

This study is not blinded. All consented PCPs will be aware of their access or lack of access to the OUD-CDS.

10.14 Participant Reimbursement

PCPs will be reimbursed $150 (PCPs without CDS access) to $300 (PCPs with CDS access) for their time to complete pre- and post-implementation surveys, and, for PCPs who have access to the CDS, to submit feedback via the feedback tab in the CDS.

10.15 Retention Plan

PCP engagement with the OUD-CDS will be measured by OUD-CDS use reports that determine for what percent of eligible encounters PCPs are using the CDS tool. These reports are provided

to both the PCP and the study team on a weekly and then, after 6-8 weeks, on a monthly basis. For PCPs with low use rates, the study team will contact the PCP directly to determine any barriers to use and to encourage increased use.

11.0 STUDY ASSESSMENTS

11.1 Study Assessments

11.1.1 PCP Surveys

Prior to going live with the OUD-CDS, PCPs with and without CDS access will complete a baseline survey via a unique emailed link. The survey will be administered via the Survey Research Center at HealthPartners Institute via RedCap, and will be maintained in a secure HealthPartners server. This initial survey will be focused on PCP confidence in their ability to screen for, assess, diagnose, treat and refer patients with OUD appropriately, assessed via 5-point Likert scales. After the 6-month intervention, all PCPs will again be surveyed about their confidence in OUD care. Additionally, the PCPs with CDS access will 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.

SURVEY DRAFT

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 at knowing 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 certified in buprenorphine prescribing) 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 or other treatment	1	2	3	4	5

. **Post-Implementation Survey**

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

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

Very often	Often	Sometimes	Occasionally	Never

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

Very confident	Moderately confident	Somewhat confident	Not at all confident

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

Very often	Often	Sometimes	Occasionally	Never

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

Very confident	Moderately confident	Somewhat confident	Not at all confident

5. 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

6. How confident are you at knowing when to refer your patients with OUD for treatment by addiction specialists?

Very confident	Moderately confident	Somewhat confident	Not at all confident

7. (Skip if certified in buprenorphine prescribing) 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	Agree	Disagree	Strongly disagree

8. 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 or other treatment	1	2	3	4	5

NOTE: **These questions will only be present in the <u>post (6-month) surveys</u> for PCPs <u>with</u> CDS access**

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

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

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

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

Strongly agree	Somewhat Agree	Somewhat Disagree	Strongly disagree

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

Strongly agree	Somewhat Agree	Somewhat Disagree	Strongly disagree

12. 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

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

Strongly agree	Somewhat Agree	Somewhat Disagree	Strongly disagree

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

Strongly agree	Somewhat Agree	Somewhat Disagree	Strongly disagree

15. Opioid Wizard improves my office efficiency.

Strongly agree	Somewhat Agree	Somewhat Disagree	Strongly disagree

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

Strongly agree	Somewhat Agree	Somewhat Disagree	Strongly disagree

17. Opioid Wizard influences my treatment recommendations.

Strongly agree	Somewhat Agree	Somewhat Disagree	Strongly disagree

18. How useful are the following Opioid Wizard features?

Feature	Very useful	Moderately useful	Somewhat useful	Slightly useful	Not at all useful
Screening tools (TAPS)					
Diagnosis tools					
Prescribing overdose kits					
Guidance for screening for comorbidities such as alcohol use disorder, hepatitis, pregnancy					
Deciding which treatment approach is best for the patient (medication-assisted therapy by primary care, referral to an addiction specialists for medication-assisted therapy, safer use, further discussion, etc.)					
Deciding between different strategies of medication-assisted					

therapy (naltrexone vs. buprenorphine vs. methadone)					
Safety alerts for drug/drug interactions					
Urine drug screen testing reminders					

19. How could we make Opioid Wizard more useful?

_____

_____

20. 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!

11.2 PCP Use Reports

Each PCP will receive weekly use reports indicating the percentage of eligible encounters for which the OUD-CDS was opened and engaged. Eligible encounters are considered encounters in which the OUD-CDS displayed a best practice alert to the PCP, letting them know that the patient has a diagnosis of OUD, is on MAT for OUD, or may be at increased risk of OUD and the PCP should considering OUD screening. Reports will show the PCP use rates in relation to other PCPs with CDS access in order to encourage high levels of use for all PCPs. Research study team members will contact PCPs who fall below a use rate of 60% to determine if there are any issues or concerns with the OUD-CDS and to problem-solve any barriers to use.

11.3 General Measures

11.3.1 Inclusion/Exclusion

Inclusion criteria for PCPs:

a) An MD, DO, NP, or PA engaging in independent primary care of adults
b) At least schedule 3 DEA prescribing privileges
c) Voluntarily consent to participation

Exclusion criteria for PCPs:

a) Less than half-time clinical primary care responsibilities

11.4 Locator Form

We will keep a list of consented PCPs (both those who have CDS access and those who do not) 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.

11.5 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 stored in a secure analytic database.

11.6 PhenX Tier 1

We will not be utilizing the PhenX Toollkit. We will be collecting data via the OUD-CDS tool itself, with data stored in a secure server located behind multiple HealthPartner firewalls. These data are captured from Clarity, largely using standard Health Care Systems Research Network Virtual Data Warehouse data elements (Ross TR 2014).

11.7 End of Medication/End of Treatment Form

Not applicable.

11.8 Study Completion Form

Not applicable.

11.9 Measures of Primary and Secondary Outcomes

Primary Aims:

1) To program an OUD-CDS tool based on a NIDA-Blending Initiative white paper "Clinical Decision Support for Opioid Use Disorders: Working Group Report" and national guidelines (VA (VA 2015), ASAM (ASAM 2015)) for use in an EMR.

   Measure 1. Demonstrate that the OUD-CDS is functional and accurate through:
   a) Testing in the EMR test environment,
   b) Chart audit validation of CDS output, and
   c) Approval of the tool by specialty addiction physician and PCP pilot testers prior to the full rollout.

2) To descriptively analyze PCP acceptability, satisfaction and use rates high enough to demonstrate proof of concept

   Measure 2A. By the end of the 6-month pilot intervention, the monthly PCP use rate of the CDS for targeted high-risk patient encounters for PCPs with CDS access will be >60%.

   Measure 2B. By the end of the 6-month pilot intervention, >60% of PCPs with CDS access will report feeling confident in assessing and treating OUD

Measure 2C. At the end of the 6-month pilot intervention, >80% of PCPs with CDS access will rate the OUD-CDS ≥4 on a 5-point Likert scale of likeliness to recommend use of the tool to their colleagues.

Secondary Aims. We will examine the usefulness of the OUD-CDS tool by comparing pre- and post-intervention rates of screening for OUD in high-risk patients, TAPS use, OUD diagnosis, use of medication-assisted therapy, as well as treatment referral patterns, for 3 groups of PCPs: (1) those with CDS access and buprenorphine certification, (2) PCPs with CDS access but without buprenorphine certification, and (3) PCPs without CDS access.

11.10 Clinical and Safety Assessments

11.10.1 Adverse Events (AEs) and Serious Adverse Events (SAEs)

This study is being conducted at the provider level using CDS prompts for 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 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 appropriate use of the Feedback button in the CDS or email to promptly notify us about such events. We will also ask PCPs to notify us of any clinical situations where their clinical judgment differs from the CDS.

Use of the Feedback button automatically generates an email that is sent to Drs. Rossom and Sperl-Hillen and the web programming team. The research 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 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 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. This feedback will be provided to the DSMB twice during the study period or at a frequency the DSMB requests.

11.11 Compliance Measures

Each PCP will receive weekly use reports indicating the percentage of eligible encounters for which the OUD-CDS was opened and engaged. Study team members will contact PCPs who fall below a use rate of 60% to determine if there are any issues or concerns with the OUD-CDS and problem-solve any barriers to use. We will consider the OUD-CDS to be effectively implemented if it is used by PCPs in at least 60% of targeted patient encounters.

11.12 Drug Use Measures

11.12.1 Urine Drug Screen

Not applicable.

11.12.2 DSM-5 Checklist

Not applicable.

12.0 TRAINING REQUIREMENTS

12.1 Overall

Enrolled PCPs who will use the OUD-CDS will be trained on how to use the tool and the importance of using the feedback tab to let the study team know of any issues or questions to help us continue to improve the CDS. Traditionally, we have completed such trainings at in-person lunch meetings with clinic personnel, but will also consider web-based trainings depending on clinic leadership preference.

13.0 STATISTICAL DESIGN AND ANALYSES

13.1 General Design

13.1.1 Study Hypothesis

A web-based EMR-integrated point-of-care CDS tool for OUD is both feasible and usable in the primary care setting.

13.2 Primary and Secondary Outcomes (Endpoints)

Primary Aims:

1) To program an OUD-CDS tool based on a NIDA-Blending Initiative white paper "Clinical Decision Support for Opioid Use Disorders: Working Group Report" and national guidelines (VA (VA 2015), ASAM (ASAM 2015)) for use in an EMR.

   Measure 1. Demonstrate that the OUD-CDS is functional and accurate through:
   a) Testing in the EMR test environment,
   b) Chart audit validation of CDS output, and
   c) Approval of the tool by specialty addiction physician and PCP pilot testers prior to the full rollout.

2) To descriptively analyze PCP acceptability, satisfaction and use rates high enough to demonstrate proof of concept

   Measure 2A. By the end of the 6-month pilot intervention, the monthly PCP use rate of the CDS for targeted high-risk patient encounters for PCPs with CDS access will be >60%.

   Measure 2B. By the end of the 6-month pilot intervention, >60% of PCPs with CDS access will report feeling confident in assessing and treating OUD

   Measure 2C. At the end of the 6-month pilot intervention, >80% of PCPs with CDS access will rate the OUD-CDS $\geq$4 on a 5-point Likert scale of likeliness to recommend use of the tool to their colleagues.

Secondary Aims. We will examine the usefulness of the OUD-CDS tool by comparing pre- and post-intervention rates of screening for OUD in high-risk patients, TAPS use, OUD diagnosis, use of medication-assisted therapy, as well as treatment referral patterns, for 3 groups of PCPs: (1) those with CDS access and buprenorphine certification, (2) PCPs with CDS access but without buprenorphine certification, and (3) PCPs without CDS access.

14.0 RECRUITMENT

PCPs will be voluntarily recruited from HPMG and PNMG in person and via emailed invitations. We will recruit all PCPs who have or will soon have buprenorphine waivers, as they will be able to use the entirety of the OUD-CDS tool. In our invitation to participate in the study, we will inform PCPs that they will receive $150 (PCPs without CDS access) or $300 (PCPs with CDS access) each to compensate them for their time in completing emailed surveys at the beginning and end

of the 6-month pilot intervention phase (all PCPs), and for their time in submitting feedback via the feedback tab in the CDS (PCPs with access to the CDS).

15.0 RANDOMIZATION AND FACTORS FOR STRATIFICATION

PCPs who are recruited and are buprenorphine-certified will be placed into the group of PCPs who have OUD-CDS access. PCPs who are recruited and do not have buprenorphine certification will be randomized to receive or not receive access to the OUD-CDS. We will be aware of practice location, patient panel size and number of patients for whom the CDS-OUD was triggered and can analyze results based on individual practice location or panel, but given the small nature of this pilot project we do not anticipate statistically meaningful information from these factors.

16.0 PREDICTION MODELS

Not applicable.

16.1 Rationale for Sample Size and Statistical Power

16.1.1 Projected Number of Sites

This study will occur at PNMG and HPMG, both of which are divisions of HealthPartners. This pilot intervention will occur at primary care clinics at which one or more eligible PCPs have consented to participate. We anticipate a total of 37-43 PCPs from twenty primary care clinics will participate.

16.1.2 Projected Number of Participants per Site

We anticipate 37-43 PCPs from approximately twenty primary care clinics will participate.

16.2 Statistical Methods for Primary and Secondary Outcomes

This pilot study for OUD-CDS feasibility and usability will not have a statistical endpoint. Provider characteristics, patient characteristics, and OUD-CDS use rates will be tracked and described. Pre- and post-intervention surveys of provider confidence in OUD assessment and treatment as well as satisfaction and usability of the OUD-CDS will be described.

16.3 Significance Testing

This pilot study for OUD-CDS feasibility and usability does not entail statistical testing or power calculations. Provider characteristics, patient characteristics, and OUD-CDS use rates will be tracked and described.

16.4 Types of Analyses

Provider characteristics, patient characteristics, and OUD-CDS use rates will be tracked and descriptively analyzed.

16.5 Interim Analysis

Not applicable for a pilot study that will be in the field for 6 months.

16.6 Exploratory Analysis

MAT has been shown to reduce adverse outcomes, such as overdoses, hospitalizations and deaths, for patients with OUD (Mohlman 2016; WHO 2013). As a quality measure to inform future implementation studies of this OUD-CDS, we will collect available EHR data to examine overdoses, ER visits, hospitalizations and deaths for patients with OUD treated by PCPs with and without CDS access. While this information will likely not be useful for statistical considerations, trends observed could be hypotheses-generating and inform future study needs.

16.7 Missing Data and Dropouts

All eligible providers may not respond to surveys or to particular survey questions. In order to minimize survey non-response we will administer the survey electronically in a format that will prompt PCPs to answer missed questions. We will also send multiple reminders of the survey and provide PCPs who do not have CDS access an incentive of $150 to complete baseline and 6-month surveys, and PCPs who do have CDS access an incentive of $300 to complete baseline and 6-month surveys and submit feedback via the CDS feedback tab.

16.8 Demographic and Baseline Characteristics

Baseline demographic and practice variables (e.g., years in practice, size of patient panel, etc.) will be summarized for PCPs enrolled in this study.

16.9 Safety Analysis

In this pilot study, we are not trying to change the standard of care for OUD treatment in primary care, but rather helping PCPs achieve this standard of care in OUD treatment. PCPs are trained that, as with other CDS 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 encounter, and PCPs are trained to let the research team know via the Feedback tab in the CDS when their clinical judgment is inconsistent with the CDS recommendations. This feedback will be monitored by the treatment team and the CDS algorithms adjusted if indicated.

An independent CTN DSMB will monitor this study. The DSMB will communicate regarding what type of reports will be needed, as well as frequency.

17.0 REGULATORY COMPLIANCE AND SAFETY

17.1 Regulatory Compliance

This study will be conducted in accordance with the current version of the protocol, in accordance with the ethical principles outlined in the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice (GCP) Guidelines, and all other applicable regulatory requirements.

17.2 Statement of Compliance

This trial will be conducted in compliance with the appropriate protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. The participating clinic sites are all within the HealthPartners system and therefore, protocol review, consent forms, and other pertinent regulatory materials will be reviewed by approved by the HealthPartners IRB prior to participant recruitment and enrollment. While the intervention is only 6 months, appropriate annual progress reports will be submitted to the HealthPartners IRB as needed.

17.3 Institutional Review Board Approval

Prior to initiating the study, site investigators will obtain written HealthPartners' IRB approval to conduct the study. Should substantive 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, the IRB will approve all consent forms and recruitment and survey materials. Progress reports will be submitted to the IRB annually or at a frequency requested by the IRB so that continuous study approval is maintained without lapse. The lead investigator is responsible for maintaining in her research files copies of current IRB/IEC approval notice and IRB-approved consent document(s), including approval for all protocol modifications. These materials must be available at any time for audit.

17.4 Informed Consent

The informed consent process is a means of providing study information to each prospective PCP participant and allows for an informed decision about participation in the study. The informed consent form will include all of the required elements of informed consent. Every study participant is required to electronically sign a valid, IRB-approved current version of the study informed consent form prior to the initiation of any study-related procedures. The site will maintain the electronically signed informed consent for every participant on a secure server that is in compliance with the HealthPartners IRB and institutional policies. Every study participant will have the opportunity to print or save a hard copy of the electronic consent form.

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

The informed consent form 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. The participant 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 or who withdraw from the study will be treated without prejudice. Study sites will be responsible for maintaining signed consent forms as source documents for quality assurance review and regulatory compliance.

17.5 Quality Assurance and Safety 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 6-month pilot phase, data will be repeatedly tested to ensure all data elements necessary for analysis are collected on secure servers, and Dr. Crain will conduct periodic test analyses to ensure that all of the data she requires for analysis are complete. Additionally, Drs. Rossom and Sperl-Hillen will conduct periodic chart audits to ensure that data collected by the CDS is accurate and complete. Drs. Rossom and Sperl-Hillen will also monitor all PCP feedback during the intervention, work together with the programming team to determine whether the CDS needs to be altered to address the issues raised in the feedback, and make adjustments to the CDS as clinically indicated.

17.6 Confidentiality

Confidentiality will be maintained in accordance with all applicable federal and state regulations. 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, 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. 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.

17.7 Health Information Portability Accountability Act (HIPAA)

Participants in this study are answering surveys regarding usability of an OUD-CDS. No personal health information is collected from participants as a part of this study. The OUD-CDS will be used by PCPs in the course of routine medical care. The CDS has automated algorithms to identify patients for whom it may be appropriate to use the OUD-CDS. These patients are not participants in the research but their data is utilized by the OUD-CDS. HIPAA itself makes specific provision for waiver of authorization to use PHI for research recruitment purposes under some specific conditions, all of which this study meets: “For research uses and disclosures of PHI, an IRB or privacy board may approve a waiver or an alteration of the authorization requirement in whole or in part. A complete waiver occurs when the IRB or privacy board determines that no authorization is required for a covered entity to use and disclose PHI for a particular research project. A partial waiver of authorization occurs when an IRB or privacy board determines that a covered entity does not need authorization for all PHI uses and disclosures for research purposes, such as disclosing PHI for research recruitment purposes. An IRB or privacy board may also approve a request that removes some PHI, but not all, or alters the requirements for an authorization (an alteration).” See:

http://privacyruleandresearch.nih.gov/pr_08.asp#8c.

17.8 Investigator Assurances

Health Partners maintains a current Federal Wide Assurance (FWA) with the DHHS Office for Human Research Protection setting forth the commitment of the organization to establish

appropriate policies and procedures for the protection of human research subjects. This documentation will be 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(b) and (f)). Prior to initiating the study, the principal investigator will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

17.9 Financial Disclosure

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.

17.10 DEA Registration (Component for medication studies using controlled substances studies – use if applicable)

All enrolled PCPs will have appropriate DEA registration. As this is required for them to be able to prescribe medications as part of their medical practice at Park Nicollet and HealthPartners clinics, research staff will not verify or monitor DEA registration status of participants. We will not be receiving any shipments of study drug.

17.11 IND Requirements (Component for IND studies – use if applicable)

Not applicable.

17.12 Clinical Monitoring

Drs. Rossom and Sperl-Hillen will monitor all PCP feedback during the intervention, work together with the programming team to determine whether the CDS needs to be altered to address the issues raised in the feedback, and make adjustments to the CDS as clinically indicated. Drs. Rossom and Sperl-Hillen will also conduct periodic chart audits during Phase 2 to determine that data collected by the CDS is accurate and complete, and that all relevant clinical information is correctly identified and used by the CDS.

17.13 Inclusion of Women and Minorities

Enrollment is at the provider level. We anticipate enrolling about 21 PCPs who will have access to the CDS and 16 PCPs who will not, and that these PCPs will be generally representative of the HPMG and PNMG provider pools in terms of gender and racial/ethnic distribution.

17.14 Regulatory Files

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

17.15 Records Retention and Requirements

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked for regulatory document compliance prior to study initiation, throughout the study, as well as at study closure. Regulatory and other research records should be maintained by the investigator 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 Lead Investigator must be notified in writing and acknowledgment must be received by the site prior to the destruction or relocation of research records.

17.16 Reporting to Sponsor

The site principal investigator agrees 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. At the completion of the trial, the Lead Investigator will provide a final report to the Sponsor.

17.17 Audits

The Sponsor has an obligation to ensure that this trial is conducted according to good research practice guidelines and may perform quality assurance audits for protocol compliance. The Lead Investigator and authorized staff from the NorthStar Node; the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN, the study sponsor); NIDA's contracted agents, monitors or auditors; and other agencies such as the Department of Health and Human Services (HHS), the Office for Human Research Protection (OHRP) and the sites' Institutional Review Board may inspect research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety.

17.18 Study Documentation

Study documentation includes all source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Committee correspondence and approved consent form and signed participant consent forms. Source documents include <u>all</u> 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.

17.19 Protocol Deviations

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.

Since the intervention of this study is access to the OUD-CDS and pre- post-intervention surveys, we do not anticipate safety issues related to the participants or for the opportunity for protocol deviations. Because the OUD-CDS programming may have unanticipated bugs that may lead the CDS to recommend (or fail to recommend) a clinical action that is inappropriate for a given patient, we will use a live “Feedback” tab that displays in the OUD-CDS to let the study team know of any questions or concerns with the CDS. This automatically generates an email that is sent to Drs. Rossom and Sperl-Hillen and the web programming team. The research team will then discuss this feedback and any necessary actions, and will connect with the PCP to answer the question, discuss steps taken to address the issue, or gather additional information and further trouble-shoot. Identification of protocol deviations through this mechanism will be adjudicated by this team who will also develop a corrective action plan for both major and minor deviations as appropriate. Those corrective action plans may be reviewed/approved by the Lead Node with overall approval by the site’s IRB. 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.

17.20 Safety Monitoring

17.20.1 Data and Safety Monitoring Board (DSMB)

An independent CTN DSMB will monitor this study. The DSMB will communicate regarding what type of reports will be needed, as well as frequency. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine 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).

17.20.2 Adverse Events (AEs)

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. To monitor usability, PCPs will be instructed to use the “Feedback” tab that displays in the OUD-CDS to let the study team know of any questions or concerns with the CDS. In particular, PCPs are trained to let the research team know via the Feedback tab in the CDS when their

clinical judgment led them to a different action than that suggested by the CDS. This automatically generates an email that is sent to Drs. Rossom and Sperl-Hillen and the programming team. The research 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, 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. This PCP feedback will be provided to the DSMB at a frequency the DSMB requests.

18.0 DATA MANAGEMENT

Apart from data collected from the PCPs via surveys and feedback mechanisms, data for analysis will be largely collected by the OUD-CDS itself. This web-based tool houses the algorithms, communicates with and displays within the EMR, and stores data required to assess study objectives will be retained in a secure analytic database at HealthPartners Institute. These data, supplemented by Epic Clarity data, will be used to assess CDS use rates, MAT rates and referral patterns (described in secondary aims). We will not be using Advantage eClinical to collect or house data, and as this is a pilot study at one medical group, we will not use a centralized Data and Statistics Center.

18.1 Study Timeline

CTN Protocol Milestone		Expected Date Completed	Comments
Protocol Development	**Concept finalized**		
	Submit protocol including DSMP and informed consent in preparation for DSMB meeting (also- site selection plan, leadership plan, proposed budget, single IRB plan, recruitment and retention plan)	2/28/2017	Final protocol and other materials due to CCTN at least one month prior to DSMB meeting.
	DSMB Meeting/Review	3/27/2017	*tentative target date, exploring what type of review required
	Full protocol reviewed and approved by NIDA	4/18/2017	* if significant changes are required following the DSMB meeting, dates will need to be adjusted
	Budget finalized	5/31/2017	
Pilot Study Stages and Milestones	Protocol approved by NIDA for implementation	4/18/2017	*Assuming quick DSMB and CCTN feedback*
	Lead Node initial Protocol IRB submission	3/1/2017	
	Initial review of all Case Report Forms by Lead Team	N/A	
	IRB Protocol approval date	4/30/2017	

CTN Protocol Milestone		Expected Date Completed	Comments
	Registration in clinicaltrials.gov website	5/15/2018	
	Stage 1 (CDS Build)	6/6/2018	
	Includes: Adapt OUD CDS whitepaper to CDS algorithms Program algorithms Create provider CDS interfaces Test algorithms in testing environment Recruit PCPs, administer baseline survey Pilot test/modify intervention with one provider with experience in OUD assessment and treatment, and several les experienced providers		
	Phase 2 (CDS Deployment)	11/7/2018	
	Includes: Go Live: Active intervention phase Monitor CDS use with feedback Update and/or troubleshoot algorithms		
	Phase 3 (Analysis and Reporting)	4/30/2019	
	Includes: Conduct follow-up provider surveys Consolidate/analyze data to test hypotheses Dissemination activities, manuscript submission		
	Final Study Report submitted to NIDA	4/30/2019	
	Provide study results via clinicaltrials.gov website (at the end of a trial)	4/30/2019	
	Primary outcome paper submitted to journal	4/30/2019	
	Primary outcome paper accepted	8/31/2019	
	Data posted on CTN's Public Data Share	10/31/2020	

19.0 PUBLICATIONS AND OTHER RIGHTS

The authors agree to follow NIH's policy requiring all investigators to submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final peer-reviewed manuscripts upon acceptance for publication, to be made publically available no later than 12 months after the official date of publication.

20.0 SIGNATURES

SPONSOR'S REPRESENTATIVE (CCTN DESIGNEE)

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version X 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 (DHHS), the state, and the IRB.

SITE'S PRINCIPAL INVESTIGATOR

Printed Name	Signature	Date

Clinical Site Name _____

Node Affiliation _____

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22.0 APPENDIX A: ADVERSE EVENT REPORTING AND PROCEDURES

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. To monitor usability, PCPs will be instructed to use the “Feedback” tab that displays in the OUD-CDS to let the study team know of any questions or concerns with the CDS. In particular, PCPs are trained to let the research team know via the Feedback tab in the CDS when their clinical judgment led them to a different action than that suggested by the CDS. This automatically generates an email that is sent to Drs. Rossom and Sperl-Hillen and the programming team. The research 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, 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.

23.0 APPENDIX B: DATA AND SAFETY MONITORING PLAN

23.1 Brief Study Overview

This study aims to program and pilot test an opioid use disorder (OUD) clinical decision support (CDS) tool in primary care clinics at HealthPartners and Park Nicollet medical groups. The CDS is based on the NIDA-Blending Initiative white paper, "Clinical Decision Support for Opioid Use Disorders: Working Group Report," and will be programmed for use in an electronic medical record (EMR) and tested by consented primary care providers (PCPs) across the healthcare system. Success of these aims will be measured by high PCP use and satisfaction rates. The secondary objectives of this pilot study are to evaluate the usefulness of the tool by comparing pre- and post-intervention OUD case-finding, medication-assisted therapy (MAT) and referral patterns for PCPs with and without CDS access.

23.2 Oversight of Clinical Responsibilities

Site Principal Investigator

The Lead Investigators are responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified, trained research staff and medical clinicians to assess, report, and monitor adverse events.

CCC Medical Monitor

It is not anticipated that a CCC Medical Monitor will be assigned to this pilot study, although this will be determined by the DSMB. Additionally, Drs. Rossom and Sperl-Hillen and the programming team will monitor all PCP feedback and make adjustments to the CDS as clinically indicated.

Data and Safety Monitoring Board (DSMB)

An independent CTN DSMB will monitor this study. The DSMB will communicate regarding what type of reports will be needed, as well as frequency. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine 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).

Quality Assurance (QA) Monitoring

It is not anticipated that this study will be assigned a NIDA CCTN CCC monitor. 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 6-month pilot phase, data will be repeatedly tested to ensure all data elements necessary for analysis are collected on secure servers, and Dr. Crain will conduct periodic test analyses to ensure that all of the data she requires for analysis are complete. Additionally, Drs. Rossom and Sperl-Hillen will conduct periodic chart audits to ensure that data collected by the CDS is accurate and complete.

23.3 Management of Risks to Participants

Confidentiality

Confidentiality of participating PCPs will be secured by the use of study codes for identifying participants on CRFs, and secure storage of any documents that have participant identifiers on site, as well as secure computing procedures for entering and transferring electronic data. The documents or logs linking the study codes with the study participant on site will be kept locked separately from the study files and the medical records. PCPs will receive reports of their use of the OUD-CDS, and these will not be confidential. Additionally, PCPs will be asked to provide feedback on the OUD-CDS, either by using the feedback tab in the CDS or via email, and this feedback will not be confidential. No identifying information will be disclosed in publications or presentations.

Information Meeting Reporting Requirements

The consent form will specifically state the types of information that are required for reporting and that the information will be reported as required.

Participant Protection

This is a pilot study that will provide OUD-CDS to approximately half of consented 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.

Pregnancy

Not applicable.

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 MAT in high risk situations; however, the risks of MAT are generally considered lower than untreated OUD in high-risk situations.

23.4 Data Management Procedures

As this is a single-site pilot study, we will not be using a centralized Data and Statistics Center or Advantage eClinical to collect or house data. All data will be stored on secure servers behind multiple firewalls at HealthPartners Institute in a secure project folder only accessible by authorized study personnel.

23.4.1 Data and Statistics Center Responsibilities

Not applicable.

23.5 Data Collection and Entry

Data from surveys completed by PCPs at baseline and 6-months and PCP CDS use will be collected and stored on a secure server protected by multiple firewalls at HealthPartners Institute, only accessible by authorized personnel only after entering highly secure system passwords.

23.6 Data Monitoring, Cleaning and Editing

Data will be monitored, cleaned and edited at HealthPartners Institute on secure servers and accessible only by study personnel.

23.7 Data Lock and Transfer

Not applicable for this single site pilot study.