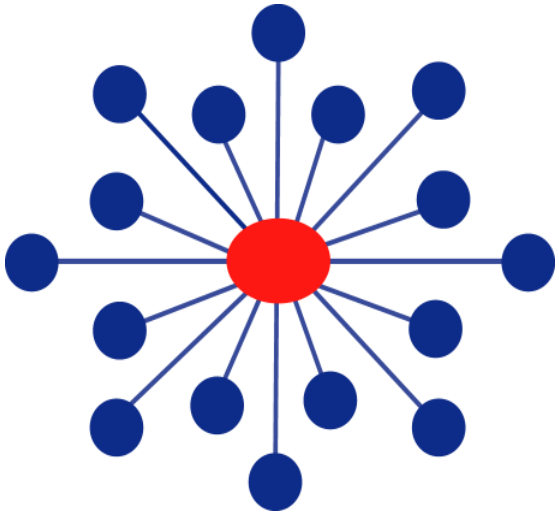

NIDA CTN Protocol 0096

Culturally Centering Medications for Opioid Use Disorder with American Indian and Alaska Native Communities

(Tribal MOUD)

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Funded by: National Institute on Drug Abuse (NIDA)
July 2, 2021
Version 2.0

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CONFIDENTIALITY STATEMENT

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ADAPT-ITT	Assessment, Decision making, Adaptation, Production, Topical experts – Integration, Training, & Testing
AI/AN	American Indian or Alaska Native
CBPR	Community-Based Participatory Research
CCC	Clinical Coordinating Center
CCTN	Center for the Clinical Trials Network
CFR	Code of Federal Regulations
CFIR	Consolidated Framework for Implementation Research
CoC	Certificate of Confidentiality
CRA	Clinical Research Associate
CRA	Community Reinforcement Approach
CRAFT	Community Reinforcement and Family Training
CRF	Case Report Form
CSM	Clinical Study Manager
CSP	Culturally Specific Prevention
CTN	Clinical Trials Network
DM	Data Management
DSC	Data and Statistics Center
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
DSMB	Data and Safety Monitoring Board
DUA	Data Use Agreement
eCRF	Electronic Case Report Form
ED	Emergency Department
EDC	Electronic Data Capture
EMR/EHR	Electronic Medical Record (or Electronic Health Record)
EPIS	Exploration, Preparation, Implementation, and Sustainment
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GLMM	Generalized Linear Mixed Model
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HSP	Human Subjects Protection
ICH	International Council for Harmonisation
IRB	Institutional Review Board
LI	Lead Investigator
MOP	Manual of Procedures
MOUD	Medications for Opioid Use Disorder (i.e., FDA-approved medications – methadone, buprenorphine (buprenorphine/naloxone), naltrexone)
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NYSPI	New York State Psychiatric Institute
OD	Overdose
OHRP	Office for Human Research Protections
OUD	Opioid Use Disorder

PI	Principal Investigator
PHI	Protected Health Information
PII	Personally Identifiable Information
PRB	Protocol Review Board
PTSD	Posttraumatic Stress Disorder
QA	Quality Assurance
RAP-C	Research Advisory Panel of California
RE-AIM	Reach, Effectiveness - Adoption, Implementation, Maintenance / Sustainability
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
SUD	Substance Use Disorder
TES	Therapeutic Education System
UDS	Urine Drug Screen

2.0 GLOSSARY OF TERMS

Acculturation	First defined as “phenomena which result when groups of individuals having different cultures come into continuous first hand contact with subsequent changes in the original culture patterns of either or both groups” (Redfield et al. 1936, p. 149); usually a marginalized group adopting culture of mainstream group.
Consumer	While “patient” is commonly used in medical settings, it can be experienced as highlighting the power differential with the clinical provider. The term “consumer” will be used in this protocol to emphasize that an individual with substance use disorders (SUD) has choices of programs and services and that the relationship between provider and consumer strives for partnership and shared decision-making.
Cultural Adaptation	“Systematic modification of an evidence-based treatment or intervention protocol to consider language, culture, and context in such a way that it is compatible with the client’s cultural patterns, meaning, and values.” (Bernal et al., 2009, p. 362)
Enculturation	“The adoption and maintenance of behaviors, norms, values, and customs from a person’s culture of origin.” (Smokowski et al., 2017)
Historical Trauma	“Cumulative emotional and psychological wounding across Generations, including the lifespan, which emanates from massive group trauma.” (Brave Heart, 1998)
Medication	Pharmacological, synthetic substances to treat illness, with an emphasis on methadone, buprenorphine, naltrexone/vivitrol.
Medicine	American Indian or Alaska Native (AI/AN) traditional use of plants and minerals, often powdered, cooked, or via teas
Microaggressions	“Subtle, stunning, often automatic, and non-verbal exchanges which are ‘put downs’.” (Pierce et al., 1978, p. 66)
Relative	Refers to the person seeking SUD services (often referred to as “patient,” “client,” or “consumer”) based on a preference by some AI/AN treatment programs to relate to the person via clan relationships as a more traditional and appropriate way to interact with one another. In this protocol, we will use “consumer” to bridge the gap between western science reviewers (and likely many urban healthcare and addiction treatment programs) and traditional AI/AN people on our research team or the people we seek to serve.

3.0 STUDY SYNOPSIS

3.1 Study Objectives

This is a **two-phase** formative research study to develop and test a program-level implementation intervention for healthcare and addiction specialty settings to provide medications to treat opioid use disorder (OUD) with American Indian / Alaska Native (AI/AN) consumers. The objective of **Phase I** is to develop a culturally centered implementation intervention to support the integration and uptake of medications for OUD (MOUD). The objective of **Phase II** is to conduct a preliminary test of the implementation intervention in four healthcare/addiction specialty treatment sites serving AI/AN communities. Community Based Participatory Research (CBPR) methods will be used in both phases. Sites will be selected during Phase I to incorporate staff from those sites into the CBPR process as part of a Collaborative Board.

3.2 Phase II Study Design and Outcomes

The study design for **Phase II** is a cluster randomized stepped wedge implementation trial with two steps, and two sites per step (N=4 sites total). Study design and methods are informed by the **C**onsolidated **F**ramework for **I**mplementation **R**esearch (CFIR; Damschroder et al., 2009) and the RE-AIM framework (Glasgow et al., 1999). RE-AIM describes key public health impact related to implementation research: 1) **R**each – proportion of people who are affected by the intervention; 2) **E**ffectiveness – positive and negative individual behavioral, quality of life, satisfaction, and physiologic outcomes of the intervention; 3) **A**doption – proportion and representativeness of participating and non-participating providers/settings; 4) **I**mplementation – extent to which the intervention is delivered as intended; and 5) **M**aintenance (or Sustainability) – the extent to which intervention becomes part of routine practice.

The primary outcome of the trial is the number of consumers with OUD initiated onto MOUD (i.e., buprenorphine, extended-release naltrexone, or methadone) in the 6 months after intervention delivery (compared to the 6 months before intervention delivery) – capturing implementation intervention Reach. Secondary outcomes include implementation and clinical endpoints: (a) number of consumers with OUD offered MOUD; (b) number of consumers screened for OUD out of overall number of new consumers; and (c) number of consumers screened with OUD retained in care for at least 3 months. Primary and secondary outcomes will be measured at the end of the six-month implementation stage and compared to the pre-intervention observation phase (prior to delivery of the implementation intervention). Primary data collection will use de-identified data from the electronic medical records (EMR; or equivalent) at each site beginning with data from the six months prior to intervention delivery for Step 1 sites and 12 months prior for Step 2 sites. For Step 1 sites, some secondary outcomes will also be assessed during the sustainment stage (the six months following implementation) – see **Figure 2** for a visual depiction of Phase II stages.

As part of the study, consumers with OUD will be asked to participate in an additional assessment study and provide informed consent. Enrolled *consumer participants* will be asked to complete four assessment visits (baseline, week 4, week 8, and week 12) to collect comprehensive information about mental health, cultural connectedness and spirituality, social functioning, and experiences with and acceptability of OUD treatment.

3.3 Sample Size and Population

3.3.1 Phase I

The Collaborative Board will be comprised of approximately 15-20 people with diverse expertise and perspectives; the Collaborative Board are not research participants. In order to incorporate perspectives on culturally centering MOUD from the four study sites, we will conduct individual qualitative interviews with approximately 8-12 consumers with previous

or current opioid use problems and 8-12 staff members. These participants will be sampled from selected sites (or associated communities). Staff and consumer participants will provide informed consent. At the end of Phase I, the implementation intervention will also be reviewed by a small number of outside (i.e., outside the Collaborative Board) experts in MOUD delivery or AI/AN culture and wellness models for objective feedback.

3.3.2 Phase II

Each of the four selected study sites should be able to assess approximately 50 AI/AN consumers per year with OUD for a total of approximately 200 consumers. De-identified data for primary and secondary outcomes will be obtained from the site's EMR (or equivalent) and thus capture all consumers with OUD who pass through the clinic. Additionally, consumers who meet criteria for OUD will be invited to enroll in an additional assessment portion of the study; we will attempt to enroll as many consumers with OUD as possible during the implementation and sustainment stages but anticipate 60-70% will agree (i.e., approximately 90-105 participants in the assessment portion of the study). A subset of enrolled consumer participants will be asked to complete a qualitative interview at the end of the assessment study. Eligible participants in the assessment portion of the study will identify as American Indian or Alaska Native (AI/AN). In addition, staff at each site will be asked to complete brief surveys during Phase II; staff with direct consumer contact will be asked to complete a qualitative interview at the end of Phase II.

3.3.3 Intervention Duration

The intervention will be a program-level culturally centered implementation intervention aimed at integrating or enhancing MOUD delivery and uptake; the intervention will be developed during Phase I of the study using CBPR methods in partnership with a Collaborative Board.

During Phase II, the implementation intervention will be delivered by Lead Team staff at the four participating sites over six months (intervention stage). Following this will be six months of active implementation and in Step 1 sites only, an additional 6 months of sustainability. During the implementation and sustainment stages (Step 1 sites), or the intervention and implementation stages (Step 2 sites), sites may also participate in a virtual Learning Community (**Figure 2**).

3.3.4 Safety Reporting

The intervention in this study is a program-level implementation intervention and therefore risk of study-related adverse events is considered minimal. Four safety events will be collected given the risk of overdose (OD) among people with OUD and higher rates of suicidal behavior among AI/AN (Leavitt et al., 2018). Deaths, overdose events, suicidal ideation, emergency department (ED) visits and hospitalizations will be captured on a case report form (CRF). The sites will follow local standard operating procedures (SOPs) for managing any medical or psychiatric emergencies.

3.3.5 Analyses

3.3.5.1 Phase I

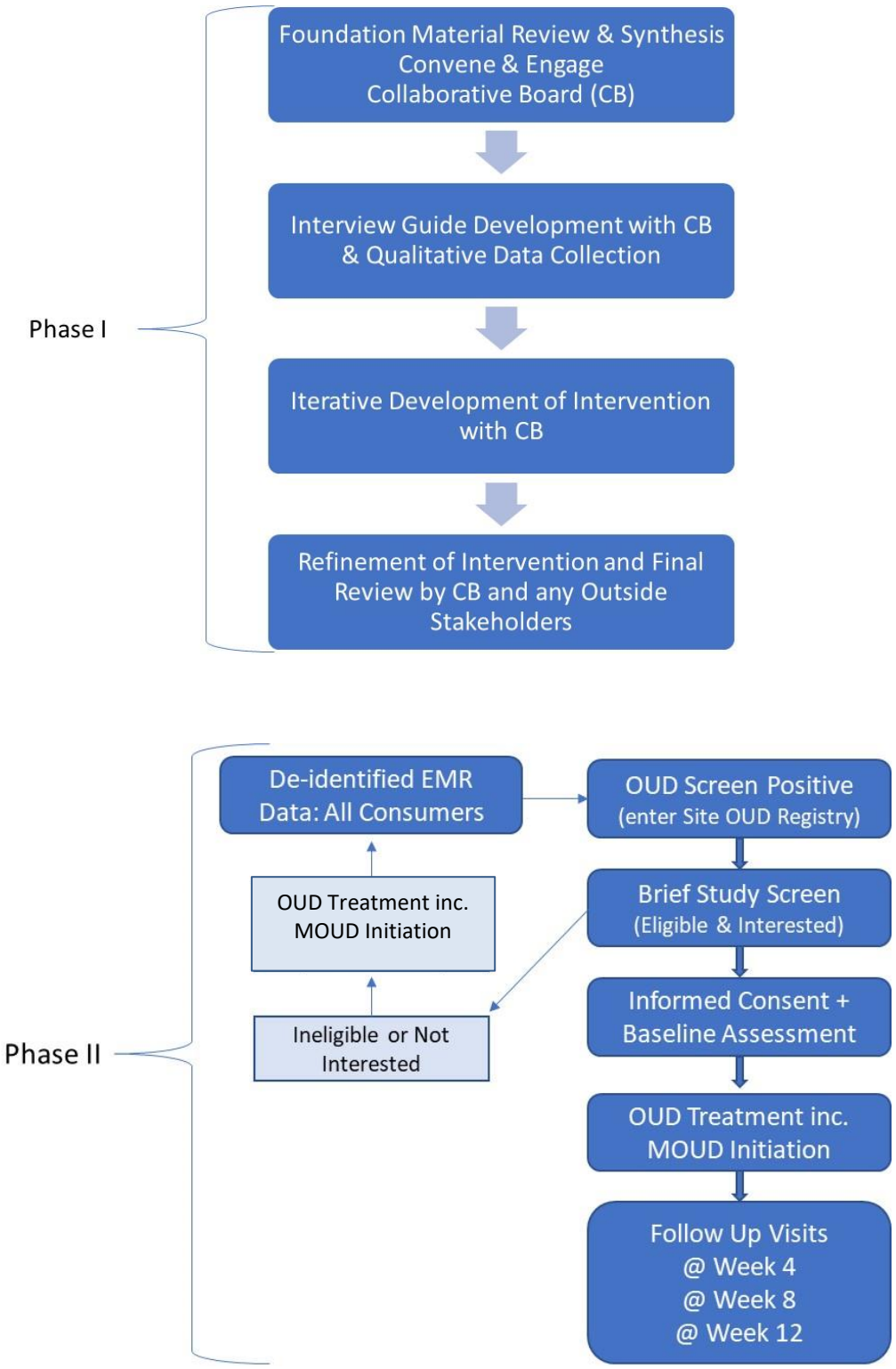
Data collected during **Phase I** will be qualitative (staff and consumer participant interviews) and used to inform intervention development. Digital recordings will be transcribed, and coded and analyzed using a qualitative analysis software package.

3.3.5.2 Phase II

Phase II will utilize a stepped wedge design where each of the four sites will be randomly selected to begin the protocol in one of two steps as illustrated in **Figure 2**. The primary outcome is descriptive in nature and involves evaluating increases in the overall number of OUD consumers that are initiated onto MOUD following the implementation stage of the study. A Poisson regression model will be used to assess the number initiated onto MOUD following intervention implementation. The model will incorporate "treatment" (pre-intervention versus implementation phase), time to recruitment (months), and clinic size because the four sites are anticipated to vary substantially with respect to size, and the number of MOUD initiations is likely associated with the total number of clinic consumers.

4.0 STUDY SCHEMA

4.1. Figure 1: Study Schema for Phase I (Development) & Phase II (Testing)



4.2 Key Research Site Roles

Each site will designate individuals in the following roles:

Key Study Role	Responsibilities	Qualifications
Site Principal Investigator (Site PI)	Oversees all research-related activities at respective sites, manages site budget, assess/monitor safety events, liaises with university-based research staff.	Medical Director (MD, NP, PA), Clinical Director or equivalent
Addiction Care Coordinator (or equivalent)	Maintains a registry of consumers with OUD, as appropriate may manage consumers prescribed MOUD in collaboration with the prescriber, and conducts research-related activities, including administering consumer participant assessments at baseline and follow-up timepoints, conducting end-of-study qualitative interviews with consumer and staff participants, and liaises with community and other methods of "publicizing" new services within the site.	RN, Social Worker, other Behavioral Health Specialist, Public Health professional, or equivalent
EMR Technician	Produces research reports and extracts relevant site data for the DSC, liaises with DSC regarding data management issues, updates EMR (or equivalent) to include new measures such as OUD screening (wherever possible).	IT Specialist, IT Programmer, or equivalent

The Lead Team will be responsible for regulatory affairs and quality assurance (QA). Lead Team Regulatory/QA personnel will manage the submission of regulatory documents to the Clinical Coordinating Center (CCC) Clinical Study Manager (CSM), and the site regulatory documents. These individuals may also be responsible for performing local QA at each site, which may be done virtually.

Lead Team Project Directors will navigate multiple study roles in Phase II, including but not limited to liaising with the sites; training study site personnel; being available to answer site questions and assist with study implementation; overseeing regulatory/QA affairs for all sites, such as correspondence with the New York State Psychiatric Institute (NYSPI) IRB, and preapproving study materials submitted to other IRBs and/or tribal review boards; developing and revising all study materials, such as consumer participant assessments, staff surveys, and qualitative interview guides; developing and managing study budgets; and coordinating study meetings.

Local Node collaborators, where applicable, will provide additional support to sites, including assistance with participant recruitment, quality assurance, and staff hiring and onboarding.

All study personnel are required to complete training as specified in the study Training Plan, in Human Subjects Protection (HSP) and Good Clinical Practice (GCP), as well as all protocol-specific training determined by the Lead Team for their research role and responsibilities. All study staff may only perform tasks and procedures for which they are adequately trained.

5.0 INTRODUCTION

5.1 Background and Significance to the Field

5.1.1 Opioid Epidemic in the United States

The US is in the midst of a devastating opioid epidemic. Since 1999, the number of OD deaths involving opioids quadrupled. In 2016, unintentional drug OD fatalities exceeded 63,000 deaths, the great majority involving opioids (Hedegaard, Warner, & Miniño, 2017). These trends are magnified among American Indian / Alaska Native (AI/AN) adults compared to other racial/ethnic groups. In 2017, AI/AN people had the second highest age-adjusted drug overdose death rates (15.7 per 100,000), with the highest occurring among non-Hispanic Whites (19.4 per 100,000; Scholl et al., 2019). With age-adjusted rates in 2015, AI/AN adults surpass OD fatalities of Whites in both metropolitan (22.1 vs 21.4/100,000 deaths respectively) and rural settings (19.8 vs 19.2/100,000 deaths respectively; Mack et al., 2017).

5.1.2 Barriers to Using Medications for OUD

FDA-approved medications for OUD (i.e., methadone, buprenorphine, and extended-release naltrexone) are considered the most effective treatment, reducing mortality and increasing abstinence and retention (SAMHSA, 2020). However, numerous barriers limit the uptake of medications for OUD in Tribal communities and within urban treatment settings serving AI/AN individuals. Common *Community factors* include stigma related to SUD and seeking treatment and perceptions of MOUD as a substitution of one drug for another (Venner, et al., 2018). Among Tribal communities specifically, additional factors include a desire for holistic treatment to include bio-psycho-social-spiritual domains and potentially community involved AI/AN traditional healing (Venner et al., 2018) and limited family and community support for MOUD. *Organizational barriers* include difficulties in attracting and retaining providers (and MOUD prescribers) especially in remote areas or on reservations, being able to provide comprehensive addiction treatment including behavioral health, lack of resources for transportation and childcare, and concerns about diversion of buprenorphine (Momper et al., 2013). In Tribal communities, these barriers may be more severe or may include a paucity of AI/AN providers and difficulty integrating or providing traditional AI/AN healing services in tandem with best practices from Western medical models. *Individual barriers* to MOUD include fear of social consequences for seeking treatment, attitudes of self-reliance, cost, and pessimistic attitudes toward treatment efficacy (or misperceptions of how MOUD works). Unique barriers may include low acceptability of strictly Western medical models of treatment and programs with few AI/AN staff or consumers (Venner et al., 2012).

5.1.3 Culturally Centering MOUD

It is incumbent to acknowledge similarities and differences between Western medical models and traditional AI/AN healing (Gone & Calf Looking, 2011; Walters & Simoni, 2002). While both aim to improve health, Western treatment is commonly secular and reductionist, while AI/AN healing focuses on holistic wellness, specifically incorporating spirituality. There is a need to explore ways to integrate Western and Indigenous health perspectives to successfully address AI/AN opioid-related health disparities and promote best outcomes.

Treatments developed specifically for cultural or ethnic groups and those adapted to be more culturally congruent have been shown to produce superior outcomes (Griner & Smith, 2006; Hall et al., 2016). Determining how and for whom an intervention is most effective is important not only in providing personalized care, but also in fulfilling the US government's trust responsibility to enhance access to culturally appropriate and effective treatment (Getches, Wilkinson & Williams, 2005; Gone & Trimble, 2012). Cultural centering is especially important in implementation of evidence-based treatments for SUD (Aguilera & Plasencia, 2005; Barrera et al., 2013).

Specifically, AI/AN populations benefit from treatments that reflect their heritage (Gone & Calf Looking, 2011), make connections to tradition, and acknowledge historical oppression, trauma, and cultural eradication (Morgan & Freeman, 2009). In addition, culturally centering evidence-based interventions increases engagement and retention of participants (Hall et al., 2016), acknowledges the fact that cultural factors impact behavioral health, and respects and revitalizes the cultural relevancy of the intervention leading to increased effectiveness (Watts, 2001, Burlew, Copeland, Ahuama-Jones & Calsyn, 2013). Thus, a culturally centered implementation process to facilitate the use of MOUD is a necessary component of effective addiction treatment with AI/AN communities.

Examples of the processes of cultural adaptations of evidence-based treatments among AI/AN communities include employing a Community-Based Participatory Research (CBPR) approach with a Collaborative Board that has on its membership community leaders, stakeholders and elders to assist with integrating the values, language and community context into the intervention and implementation (Jernigan, D'Amico, Duran, & Buchwald, 2018). In addition, many Tribal-academic partnerships have conducted focus groups to tailor components for cultural and contextual fit (Novins et al., 2012; Hirchak et al, 2018). Other researchers and Tribal communities have adapted interventions through the guidance of a medicine person (Beckstead et al., 2015) along with a Tribal counselor and Tribal council (Venner et al., 2016) and maintained fidelity to the adapted version through trainings and weekly calls. Academics and Tribal communities have also made surface and deep structural adaptations delivering interventions in the Native language and integrating the values and local culture into the intervention (Ivanich et al., 2018).

Specific cultural activities like talking circles, drumming, and sweat lodges have been integrated into existing substance use treatments specific to the local culture and the needs of Native individuals seeking care (Dickerson et al., 2014; Gossage et al., 2003; Woodall, Delaney, Kunitz, Westerberg, & Zhao, 2007). Key to implementing cultural adaptations are the training and hiring of Native, local community members to implement the intervention (Venner et al, 2016; Gray, 2010).

There is burgeoning research specifying the processes of cultural adaptation (Domenech Rodriguez et al., 2011). The primary models used with AI/AN populations are: Culturally Specific Prevention (CSP; Whitbeck, 2006) and ADAPT-ITT (**A**ssessment, **D**ecision making, **A**daptation, **P**roduction, **T**opical experts – **I**ntegration, **T**raining, & **T**esting; Wingood & DiClemente, 2006). The CSP model emphasizes determination of risk and protective factors from research with the specific ethnic group followed by cultural translation and measurement of such factors, culminating in clinical trials to test the adapted intervention. ADAPT-ITT has been employed to culturally adapt the Therapeutic Education System (TES) with AI/AN adults, a digital therapeutic grounded in the Community Reinforcement Approach (CRA) (Campbell et al, 2015) and in Motivational Interviewing and CRA (Venner et al, 2016). These cultural adaptation models are iterative approaches that involve community members and experts in the evidence-based treatment to incorporate important cultural elements while maintaining fidelity to the core theories and content of the intervention.

Culturally centered MOUD services have been successfully implemented with Indigenous people in Australia and Canada by incorporating culturally-specific designs, integrated care, and an emphasis on family and community wellness (Black et al., 2007; Poirier, 2015; Williams et al., 2006). Developing culturally appropriate and effective interventions with AI/AN communities requires an approach that includes reciprocity between academic and community researchers. Community-based and Tribal participatory research approaches are respectful and effective ways for academic and Tribal communities to develop trust and collaborate through all phases of the research process (Cochran et al., 2008; Fisher & Ball, 2003; Lowe et al., 2011). Thus, the objective of this proposal is to work in collaboration with AI/AN clinicians, researchers, community

members, consumer advocates and others to develop a culturally centered program to implement MOUD.

5.1.4 Study Rationale

The opioid epidemic has disproportionately impacted AI/AN communities. MOUD is a first line treatment for managing OUD and reducing mortality associated with opioid OD. Uptake of MOUD in healthcare and addiction treatment settings serving AI/AN communities has been slow for a number of reasons, including a disconnect between Western medical models of treatment (i.e., MOUD) and Indigenous wellness paradigms, including traditional healing practices. Integrating MOUD within a culturally centered implementation intervention may improve the acceptability and uptake of MOUD among AI/AN-serving providers and AI/AN consumers with OUD.

The goals of this study are (1) to develop a culturally centered implementation intervention using CBPR methods and (2) to test the implementation intervention within four healthcare/addiction specialty programs serving AI/AN communities in a two-year stepped wedge design on the primary outcome of number of consumers with OUD initiated onto MOUD in the 6 months after intervention delivery (compared to pre-intervention). A stepped wedge design will allow for all four sites to implement the intervention while exploring implementation and clinical outcomes.

6.0 OBJECTIVES

6.1 Primary and Secondary Objective

6.1.1 Phase I

The primary objective of Phase I (approximately 12 months) is to develop a culturally centered implementation intervention using CBPR methods.

6.1.2 Phase II

Primary Outcomes: The primary objective of Phase II (approximately 24 months) is to conduct a preliminary test of the implementation intervention in four healthcare programs serving AI/AN communities. The study design is a cluster randomized stepped wedge with two steps and two sites per step. The primary outcome of the trial is the number of consumers with OUD initiated onto MOUD in the 6 months after intervention delivery (compared to pre-intervention). Primary outcome data will be extracted from the EMR (or equivalent) at each participating site.

Secondary Outcomes: Secondary outcomes will also be derived from the EMR (or equivalent) at each participating site and include: (2a Implementation) number of consumers with OUD offered MOUD; (2b Implementation) number of consumers screened for OUD of the overall number of new consumers; and (2c Clinical) number of consumers with OUD retained in care for at least three months. Secondary outcomes will be measured during the 6-month implementation phase and compared to the pre-intervention observation phase.

For Step 1 sites, analyses will also be conducted to compare pre-intervention observations versus sustainment observations (i.e., the six months following implementation).

6.2 Exploratory Objective(s)

6.2.1 Phase II

Exploratory analyses will test for differences based on potential organizational predictors of primary and secondary outcomes to include organizational characteristics (e.g., rural/reservation vs. urban/suburban settings; program size; co-location of behavioral health or addiction treatment in primary care; staff attitudes, beliefs, social norms). Additional consumer-level characteristics (e.g., sex, psychological distress, cultural identity, spirituality) will also be explored as potential moderators of clinical outcomes based on participants enrolled in the assessment portion of the study (as opposed to data collected at the program level).

7.0 STUDY DESIGN

7.1 Overview of Study Design

7.1.1 Design Overview

Proposed is a two-phase development and testing of a culturally centered program-level implementation intervention to integrate MOUD in four healthcare/addiction specialty settings using a stepped wedge randomized study design. See **Figure 2** for Phase II Study Timeline and Activities. Two models form the conceptual foundation of this proposal. The **Consolidated Framework of Implementation Research (CFIR)** (Damschroder et al., 2009) distinguishes multi-system targets posited to influence how and in what way successful implementation occurs. CFIR will inform targets of the implementation intervention. CFIR multi-system targets include: structural (outer setting), organizational (internal setting and process), staff and patient (individual characteristics), and intervention characteristics. For example, at the level of intervention characteristics, MOUD is conceptualized as a medication-based intervention for a chronic condition, consistent with treatments for other disorders typically delivered in primary care. At the structural (outer setting) level, state regulations may positively influence MOUD implementation by incentivizing organizations to provide integrated addiction care, although organizations will need to make MOUD delivery financially viable within their setting. Staff (i.e., attitudes, training) and organizational (readiness to change) characteristics should be considered to understand which implementation strategies might be useful, including training and coaching.

The **RE-AIM Model** (Glasgow et al., 1999) was developed as a multi-level framework to guide the evaluation of public health-related implementation. This model informs key primary and secondary endpoints. The essential outcomes are: 1) **R**each – proportion of people who are affected by the intervention; 2) **E**ffectiveness – positive and negative individual behavioral, quality of life, satisfaction, and physiologic outcomes of the intervention; 3) **A**doption – proportion and representativeness of participating and non-participating providers/settings; 4) **I**mplementation – extent to which the intervention is delivered as intended; and 5) **M**aintenance/Sustainability – the extent to which intervention becomes part of routine practice (see **Table 1** for Measures).

7.1.2 Phase I

The implementation intervention will be developed using CBPR methods in partnership with a Collaborative Board (see section 11.1 for a detailed description of procedures). The Collaborative Board will be comprised of approximately 15-20 members with diverse expertise and experience (e.g., prescribers of MOUD, behavioral health providers, AI/AN providers, AI/AN people knowledgeable in traditional healing and worldviews, AI/AN traditional healers with expertise in OUD and MOUD, AI/AN community members with diverse perspectives on MOUD, AI/AN who have resolved OUD (in recovery), and experts in clinical implementation of MOUD with AI/AN) and be convened in month 1. The four participating clinical sites will also be recruited in Phase I and approximately one to two staff people from each of the participating clinical sites will also be asked to join the Collaborative Board as part of CBPR methods, as time allows. The Collaborative Board will accomplish the following over the course of the first year: (1) review and synthesis of relevant academic and Tribal materials on providing services to AI/AN with SUD (and specifically OUD), implementation facilitation models, and evidence-based treatment adaptation models; (2) develop qualitative interview guides for use with staff and consumer interviewees; (3) develop program-level implementation intervention components; and (4) refine and finalize program-level implementation intervention components.

Additional activities during Phase I will include IRB submission(s) and approval(s) (we will ideally use a centralized single IRB, but this will be dependent on requirements of participating sites), recruitment and data collection with approximately 8-12 staff and 8-12 consumers from the

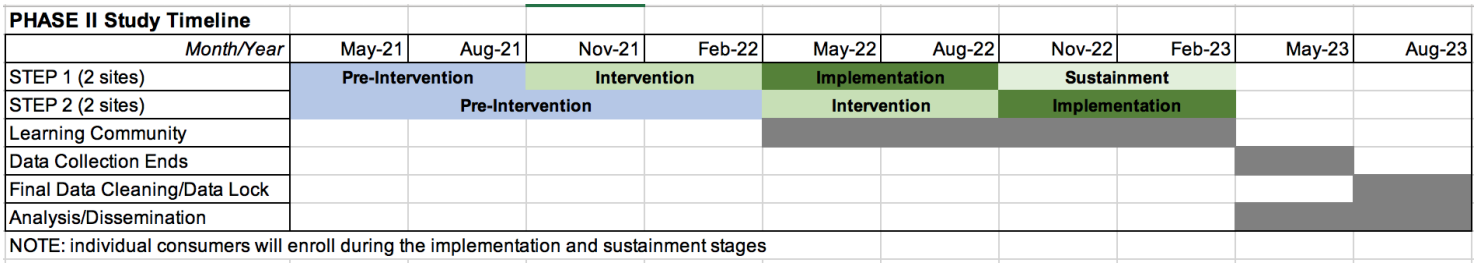
participating clinical sites (or surrounding community), and data system development (i.e., procedures for accessing program-level data from sites and assessment procedures for participants recruited during Phase II).

7.1.3 Phase II

The program-level culturally centered implementation intervention will be tested in four sites using a stepped wedge design. Sites will be randomly assigned to one of the two steps. The primary outcome is the number of consumers with OUD initiated onto MOUD (i.e., one of the three FDA-approved medications for OUD) in the 6 months after intervention delivery (compared to the 6 months before intervention delivery). A cluster-randomized stepped wedge design was chosen to best test preliminary feasibility and efficacy of a program-level health services implementation intervention in a relatively small number of clinical sites. A program (site)-level randomized, parallel group design was considered, but such designs typically require large numbers of sites, and only half of sites would receive the implementation intervention. The stepped wedge design also allows for staggered implementation of the intervention to reduce burden of training (focused training of two sites at a time) and allows for improvements and modifications to the intervention through continuous quality improvement within sites and between Step 1 and Step 2 of Phase II, appropriate for formative research. Thus, at the end of Phase II, the intervention will be ready for wider scale up and/or additional testing.

The program-level implementation intervention will be delivered over six months, with the expectation of variability across sites in how quickly MOUD delivery is initiated or expanded. The primary outcome will be assessed following intervention delivery in a six-month implementation stage. Step 1 sites will also complete six-month sustainment stage, whereby MOUD delivery is anticipated to become more fully part of routine care.

7.1.3.1 Figure 2: Phase II Study Timeline



7.2 Duration of Study and Visit Schedule

Phase I will be approximately 12 months. Phase II will be approximately 24 months beginning in May 2021. Pre-intervention observational data will be collected for 6 months for Step 1 sites and 12 months for Step 2 sites.

Sites randomized to Step 1 will receive the 6-month program-level intervention, followed by 6-months of implementation, and 6-months of intervention sustainment. Sites randomized to Step 2 will receive the 6-month program-level intervention, followed by 6 months of implementation.

Consumer participants may be enrolled into the assessment portion of the study anytime during the implementation or sustainment phases. Enrolled consumer participants will complete four monthly assessments over 3 months. A random subset of enrolled consumer participants will also complete a qualitative interview at the 12-week assessment. Figure 2 provides a visual representation of Phase II with approximate dates.

8.0 OUTCOME MEASURES

Table 1 provides information on measures and assessment source.

8.1 Primary Outcome Measure

Primary Outcome (Implementation – Reach)	Number of consumers with OUD initiated onto MOUD based on data from site

8.2 Secondary Outcome Measures

Secondary Outcome (Implementation - Adoption)	Number of consumers with OUD offered MOUD based on data from site
Secondary Outcome (Implementation - Implementation)	Number of new consumers screened for OUD out of overall number of new consumers based on data from site
Secondary Outcome (Clinical - Effectiveness)	Number of consumers with OUD retained in care for ≥3 months based on data from site (retained yes = ≥ 1 visit per month)

8.3 Exploratory Outcomes

Clinical Effectiveness	• Mental health (depression, anxiety, and hopefulness) • Substance use (self-report and available urine toxicology) • Continuation of MOUD for ≥3 months
Staff Attitudes (Adoption)	• Staff attitudes towards MOUD • Intervention acceptability, appropriateness, and feasibility

8.4 Exploratory Predictors/Moderators

Implementation (Individual consumer participants)	• Consumer demographic characteristics • Acceptability of and attitudes towards MOUD • Cultural Identity • Spirituality • Discrimination Experiences • Historical Loss
Implementation (Inner setting, Individual Staff)	• Staff attitudes towards MOUD • Organizational readiness • Intervention acceptability, appropriateness, and feasibility • Program characteristics (e.g., size, staff turnover)

8.5 Study Timeline

See **Figure 2** for a visual of the Phase II timeline. After receiving Protocol Review Board (PRB) comments and NIDA CCTN approval of the full/final protocol, Phase I will launch. In addition to intervention development in Phase I, we will also seek IRB approval, recruit and onboard clinical sites, develop the data collection systems, develop the manual of procedures (MOP), and conduct staff training. Phase II will begin in Year 2 starting with intervention delivery in Step 1 sites. Step 2 sites will receive the intervention about half-way through Year 2. Data collection from site

consumer participants will also begin about half-way through Year 2 in Step 1 Sites and continue through Month 25. Two months will be allowed for data lock after the end of data collection. Therefore, data lock is projected to occur approximately 32 months after PRB approval of the final protocol.

Anticipated Protocol Milestones

Milestone	Approximate Month
Protocol Approved by NIDA	Month 1
IRB Approval	Month 4
Observation Period Starts	Month 7
Completion of Phase I	Month 12
Intervention Step 1 Starts	Month 13
Intervention Step 2 Starts	Month 19
Completion of Consumer Participant Recruitment	Month 28
Completion of Data Collection	Month 30
Data Lock	Month 32

9.0 STUDY POPULATION

9.1 Participant Inclusion and Exclusion Criteria

Research participants will consist of consumers and staff with direct consumer contact in Phase I and Phase II. All participants must meet all inclusion criteria in order to be eligible to participate in the study (per specific criteria for each group below). Women are included in accordance with the NIH Policy on Inclusion of Women and Minorities as Participants in Research Involving Human Subjects. Given the specific cultural focus on AI/AN people, consumer participants must self-identify as AI/AN. All individuals meeting any of the exclusion criteria at screening will be excluded from study participation.

9.1.1 Phase I

As part of Phase I activities, research staff will conduct consumer (approximately 8-12) and staff (approximately 8-12) interviews to gather information relevant to the development of the implementation intervention as determined/developed by the Collaborative Board. Interviewees will be considered research participants and will provide informed consent. Consumer and staff participants will be recruited from two of the four participating sites (and larger community associated with the site, as needed).

Individuals must meet all of the inclusion criteria and none of the exclusion criteria at screening in order to be eligible to participate in the study.

Consumer Inclusion Criteria

1. Willing and able to provide informed consent (consent process)
2. English comprehension and proficiency (consent process/consent assessment)
3. Receiving services at a participating study site or reside in a community associated with the study site (self-report)
4. Identified (screened) as having current opioid misuse or opioid use disorder or be in OUD recovery (self-report)
5. Self-identify as AI/AN (does not need to be exclusive of other racial/ethnic identification) (self-report)
6. 18 years or older (self-report)

Consumer Exclusion Criteria

Consumers will be excluded if they have a psychiatric, cognitive, or medical condition which would make participation inappropriate or contraindicated, as determined by research or clinical staff.

Staff Inclusion Criteria

1. Willing and able to provide informed consent (consent process)
2. Employed at a participating study site OR employed in a local primary care or addiction specialty treatment program (self-report)
3. Have one of the following roles (or equivalent) within the healthcare setting: physician, nurse practitioner, physician's assistant, nurse, medical technician or assistant (may include receptionists or registration staff), behavioral health provider or counselor, traditional healer, cultural educator, or peer recovery coach/specialist (self-report)

Staff Exclusion Criteria

There are no specific exclusion criteria for Phase I staff.

9.1.2 Phase II

The cluster-randomized stepped wedge study will take place in Phase II. Although most data will be drawn from the EMR (or equivalent), eligible consumers will be invited to enroll into the assessment portion of the study and complete research visits at baseline (i.e., at the point they screen positive for OUD), Week 4, Week 8, and Week 12. Each of the four selected study sites should be able to assess approximately 50 consumers per year with OUD for a total of approximately 200 consumers (during the implementation and sustainment stages). We will attempt to enroll as many consumers who screen positive for OUD as possible but anticipate 60-70% will agree (90-105 participants in the assessment portion of the study).

A subset of consumers will be invited to participate in an end-of-study qualitative interview at Week 12 (approximately 10 per site; the lead node will determine a random selection process one recruitment pace is established).

In addition, staff will be invited to complete brief (approximately 10 minutes) surveys at baseline (i.e., at the start of Step 1), after intervention delivery and after implementation and participate in an end-of-study qualitative interview. All eligible staff will be asked to participate.

Research participants include both consumers and staff with direct consumer contact. Individuals must meet all of the inclusion criteria and none of the exclusion criteria at screening in order to be eligible to participate in the study.

Consumer Inclusion Criteria

1. Willing and able to provide informed consent (consent process)
2. English comprehension and proficiency (consent process/consent quiz)
3. Receiving services at a participating study site
4. Meet criteria for a current opioid use disorder (site initiated)
5. Self-identify as AI/AN (does not need to be exclusive of other racial/ethnic identification) (screening form)
6. Willing to have program data linked to assessment data (consent process)
7. 18 years or older (self-report)

Consumer Exclusion Criteria

Given that Phase II consumers will be receiving standard care at the participating sites, the only exclusion criteria are if participation in the research assessments is contraindicated as determined by research staff (assessed through interactions with the individual during the consent process) or if they are planning to move away within the next 3 months. Specific training will be provided to research staff for administering informed consent.

Staff Inclusion Criteria

1. Willing and able to provide informed consent
2. Employed at a participating study site
3. Have direct consumer contact (administrative or clinical)

Staff Exclusion Criteria

There are no specific exclusion criteria.

9.2 Strategies for Recruitment and Retention

Four clinical programs will be recruited to participate in this study. See Section 10.0 for details on site selection.

9.2.1 Phase I: Consumer and Staff Participants

Consumers will be recruited from within the four participating sites, as available (8-12 consumers total, approximately 4-6 per site) via staff referral or flyers in the waiting room. As needed, recruitment may occur outside the participating site through flyers in local health or mental health organizations. Staff (8-12 total, 4-6 per site) will be recruited by word of mouth/announcements at staff meetings. As needed, provider recruitment may occur in other local addiction specialty or health care programs.

9.2.2 Phase II: Consumer and Staff Participants

Consumer Participants: Data will be accessed for all consumers from each of the four participating sites via the EMR (or equivalent system). These data will be used to assess primary and secondary outcomes.

Consumers consenting to and participating in the assessment portion of the study will be comprised of anyone who screens positive for an OUD, screens eligible (e.g., self-identifies as an AI/AN adult), and consents to participate. As such all consumers (program data) and consumer participants (consent to be involved in the assessment portion of the study) will be currently receiving services at the participating site. This will likely alleviate proactive recruitment outside the site. However, additional recruitment efforts will be utilized as needed to include: flyers, newspaper and newsletter announcements, outreach and linkage to local community-based organizations, treatment programs, and departments of health; word of mouth (organically by consumers) by site staff and the local community; and linkages to Tribal organizations, groups, and community events. The Collaborative Board will assist with potential recruitment strategies as needed. Recruitment into the assessment portion of the study will begin following the intervention stage of the study.

The addiction care coordinator (or equivalent) will identify consumers at participating sites who screen positive for OUD (using standard site procedures and an evidence-based screening tool). The consumer will then be asked if they are interested in completing a brief screening assessment to see if they might be eligible to participate in an assessment research study. If eligible and interested, the consumer will provide informed consent and enroll into the study.

Retention of study participants will be integrated within standard care at the participating sites and overseen by the addiction care coordinator (or equivalent). Retention efforts will include engagement and rapport-building, contact information for family or friends (as permitted by consumer), and ongoing outreach by the addiction care coordinator (or equivalent; e.g., weekly check-in calls).

Regardless of whether a participant stops receiving MOUD at a participating site, or halts their medical care in general, the addiction care coordinator (or equivalent) will continue to contact the participant and attempt to schedule follow-up assessments. If the participant is no longer receiving care at the site, research assessments may occur remotely.

Staff Participants: Recruitment into the survey portion of the study will be completed at all staff meetings (or equivalent functions or individually as needed). Surveys will take place before intervention delivery, before implementation, and after implementation. All eligible staff will be invited to participate. For the end-of-study qualitative interview, all staff (who meet eligibility criteria) will be invited to participate in the interview.

10.0 SITE SELECTION

10.1 Number of Sites

Four primary healthcare and/or addiction treatment sites will be selected to participate in the study. Site selection will occur during Phase I.

10.2 Site Characteristics

Sites need to demonstrate the following characteristics:

- Serve AI/AN consumers.
- Provide primary healthcare services (with or without co-located behavioral health or addiction treatment services) or specialty addiction treatment.
- Diversity in terms of urban and rural (or reservation) settings.
- Readiness to provide MOUD defined as wanting to initiate MOUD within 6-12 months or have already initiated MOUD but interested in expanding services and/or including cultural centering.
- For sites that have already initiated MOUD, provide MOUD to no more than 20% of their consumers with OUD.
- Able to serve (and assess) approximately 50 AI/AN people with OUD per year.
- Employ an EMR (or equivalent system) with the ability to extract primary and secondary outcome data.
- Interested in research collaboration.

10.3 Rationale for Site Selection

Inclusion criteria for study sites was determined based on consensus discussion with the protocol development team. The team specifically discussed two issues: (1) type of program to focus upon (i.e., healthcare setting providing primary care and/or addiction treatment); and (2) the preferred level of experience with MOUD and readiness to implement (i.e., from MOUD naïve sites to sites already providing MOUD but interested in expanding or incorporating cultural centering of MOUD). The decision was made to include both primary care sites and addiction specialty programs and to be flexible in terms of how far along sites were in integrating MOUD – keeping in mind the need for reasonable ability to observe changes in the primary and secondary outcomes.

Primary care and addiction specialty programs will likely have different challenges in integrating MOUD and offering culturally centered services, including incorporation of traditional healing, ceremonies and medicines. For example, primary care settings will have access to medical prescribers and use medications routinely to treat other chronic health conditions, which may reduce barriers to and increase acceptability of prescribing MOUD. Nonetheless, primary care clinics may have less accessibility to behavioral health services to help support MOUD and have less opportunity for incorporating cultural content. The opposite will likely be true for addiction specialty settings – less access to medical prescribers and potentially less experience using medications to treat chronic illness, which may contribute to greater barriers to providing MOUD.

In addition, SUD treatment counselors often subscribe to a twelve-step model that emphasizes abstinence as the target outcome; in many cases, using MOUD as part of recovery is not considered true abstinence. On the other hand, addiction specialty settings will have greater access to behavioral health providers to provide psychosocial support services related to MOUD and potentially greater integration of culturally tailored education and activities. Expanding the

types of sites in this formative implementation trial to include both primary care and behavioral health settings will allow for assessment of a wider range of barriers and facilitators and ultimately an implementation manual that can be tailored to support integration of MOUD across a wider range of programs, thus increasing ecological validity and generalization to the greatest number of programs serving AI/AN people. As possible, sites will also be selected in geographic areas with higher rates of AI/AN adult opioid OD.

11.0 STUDY PROCEDURES

11.1 Phase I: Developing the Culturally Centered MOUD with AI/AN Adults

Phase I formative work is grounded in CBPR methods and informed by community-driven intervention adaptation models. The goal of Phase I is to develop a culturally centered implementation intervention with flexibility for use in both primary healthcare settings and addiction specialty programs serving large numbers of AI/AN consumers with the goal of improving accessibility, acceptability, cultural congruence of MOUD, and ultimately uptake.

Community-Based Participatory Research (CBPR). CBPR is a "partnership approach to research that equitably involves, for example, community members, organizational representatives, and researchers in all aspects of the research process, in which all partners contribute expertise and share decision making and responsibilities" (Israel et al., 2005, p. 1464). CBPR incorporates the rigor and ethics of high-quality research while requiring community collaboration and partnership (Israel, Schulz, Parker, & Becker, 1998; Minkler & Wallerstein, 2003). CBPR grew out of the social justice movements as a tool to improve social conditions, effect change, and develop and enhance trust between communities and researchers (Horn, McCracken, Dino, Brayboy, 2008; Wallerstein & Duran, 2006). The prioritizing of social justice and equitable partnerships makes it a particularly appropriate method for collaboration with Tribal communities and other urban AI/AN-serving organizations which should enhance the acceptability and sustainability of interventions (Horn et al., 2008).

CBPR is defined by nine guiding principles (Israel et al., 2005) which will provide the foundation for the work in Phase I and II to be completed:

1. Recognize community as a unit of identity.
2. Build on the strengths and resources within community.
3. Facilitate collaborative, equitable partnerships that involve empowerment and power-sharing to attend to social inequalities.
4. Foster co-learning and capacity building.
5. Integrate and achieve balance between knowledge generation and intervention for mutual benefit of all partners.
6. Focus on local relevance of public health problems and ecologic perspectives that recognize and attend to multiple determinants of health.
7. Involve systems development using cyclical and iterative processes.
8. Disseminates results to all partners; involve all partners in the dissemination process.
9. Involve long-term process and commitment to sustainability.

We are utilizing aspects of CBPR throughout our project by including community partners on the protocol development team and the Collaborative Board. In addition, we are inviting staff and AI/AN consumers from each of the four participating sites to aid in Phase I intervention development and the subsequent testing of the intervention in Phase II. Involving the clinical sites in Phase I will also aid in relationship development, which is crucial to CBPR and successful implementation as well as interpretation and dissemination of results.

Adaptation and Adaptation Models. Cultural adaptation is especially important in implementation of interventions for addiction (Burlew, Copeland, Ahuama-Jonas, & Calsyn, 2013; Campbell et al., 2015; Legha & Novins, 2012; Aguilera & Plasencia, 2005; Hecht et al., 2003; Steiker, 2008). For example, Tribal populations may utilize coping processes unique to their culture and benefit

from services that reflect their heritage (Garroutte et al., 2009; Gone & Calf Looking, 2011; Jumper-Reeves et al., 2013; Legha & Novins, 2012; Venner, Feldstein, & Tafoya, 2008; Wexler 2014). In addition, Western models of treatment are typically individualistic, secular, and lean toward reductionism. In contrast, traditional AI/AN models of healing are more collectivistic, spiritual, and holistic in conceptions of well-being, so cultural centering will consider these aspects as well. AI/AN disparities in SUD have been attributed to a lack of connection to cultural identity and tradition, a history of oppression, and cultural eradication (French, 2004; Morgan & Freeman, 2009). Kleinman (2013) recommends that providers have a conversation with consumers about their cultural beliefs and an understanding of the etiology of symptoms for a more harmonious collaborative relationship with better health and well-being outcomes. Thus, adaptation of addiction services and treatments to integrate culturally relevant factors and better represent AI/AN values and traditions is a necessary component of effective treatment (Legha & Novins, 2012) and most respectful of and supportive of AI/AN cultural continuity (Gone, 2008). Thus, we will integrate a cultural centering of MOUD within an AI/AN healing framework rather than simply adding cultural adaptations to MOUD in the context of an implementation intervention.

In Phase I work, two cultural adaptation models will be utilized to guide the development of culturally centered MOUD with AI/AN adults: 1) ADAPT-ITT (Wingood & DiClemente, 2008) and (2) CSP Approach (Whitbeck, 2006). ADAPT-ITT was originally developed to adapt HIV risk reduction interventions among African American populations utilizing both content experts and community partnerships. It consists of eight steps starting with assessment of community need and adoption of a relevant and acceptable intervention, initial testing and feedback among stakeholders followed by topical experts, and then pilot testing the integrated adapted version of the intervention. The CSP includes reviewing existing literature and research in addition to working with the community and content experts. The five steps in CSP include identifying risk/resilience factors (strengths and challenges) in the literature and with the community, working with stakeholders to integrate relevant factors to fit cultural context, and conducting pilot testing with the culturally specific intervention. These two models inform Phase I steps and the testing of culturally centered implementation intervention.

11.1.1 Foundation: Literature/Resource Search and Synthesis (Months 1-3)

In the first several months of Phase I (see **Figure 1**), we will systematically identify, collect, and synthesize relevant materials to inform the implementation intervention components. Resource searches will be completed in the following areas:

- Implementation facilitation interventions for integrating MOUD and other addiction treatment interventions (e.g., strategies, systematic processes)
    - This will include overview of the EPIS process (Aarons et al., 2012; Moullin et al., 2019) for possible inclusion. EPIS is: exploration (needs assessment, implementation team development, champion identification), preparation (development of clinic work flow plan, tailoring of new screening and treatment materials, outreach to other community resources, including behavioral health), implementation (rapid cycle assessment of initial implementation, audit and feedback procedures), and sustainment (identification of staffing needs after the research study, development of community coalitions to support the continuum of care).
- Materials and resources specific to preventing and treating OUD within Native communities (e.g., Tribal-specific resources; Tribal best practices)
- AI/AN traditional healing practices and modalities (e.g., medicine/plants/minerals, prayers, ceremonies, sweat lodge, purification, Native American Church, peyote)

- Conceptualizing AI/AN wellness and/or healing
- Etiology of addiction for AI/AN adults (e.g., historical/generational trauma, bio-psycho-social-spiritual, genetics, brain neurocircuitry, discrimination/oppression, poverty)
- Culturally specific protective and risk factors
- Research literature on OUD and AI/AN adults, including MOUD and MOUD outcomes (e.g., qualitative and quantitative research, Tribal epi center reports, health disparities).
- Cultural adaptations of SUD within AI/AN adults (e.g., qualitative, quantitative, efficacy and effectiveness trials)
- Chronic pain and OUD/MOUD; conceptualization of pain

11.1.2 Convene Collaborative Board, Overview, Engagement (approximately Months 1-3)

The Lead Team will invite a multidisciplinary and culturally informed group of individuals to participate in a Collaborative Board to partner in developing a program-level, culturally centered MOUD implementation intervention. The Collaborative Board will include medication prescribers, behavioral health providers, AI/AN providers, AI/AN people knowledgeable in traditional healing and worldviews, AI/AN traditional healers with expertise in OUD and MOUD, AI/AN community members with diverse perspectives on MOUD, AI/AN adults who have resolved OUD (in recovery), and experts in clinical implementation of MOUD with AI/AN. In addition, we will involve people from various tribes in order to include multiple Tribal perspectives and increase generalizability to other tribes interested in implementing MOUD. The Lead Team will also request that at least one person from each of the participating four sites join the Collaborative Board, in line with the CBPR approach.

During Months 1-3, the Collaborative Board will meet approximately twice per month via conference calls. The initial call in Month 1 will be used to begin rapport building, achieve consensus on communication processes, CBPR principles, and general orientation and mission. The mission, communication processes, roles, and expectations will be written up and distributed for approval by the Collaborative Board.

The first major task of the Collaborative Board will be to review and discuss the information synthesis to a) identify key components for inclusion within a culturally centered implementation intervention program, b) identify specific implementation strategies and processes and how they need to be culturally adapted, and c) gaps in knowledge. This discussion will incorporate key domains from the CFIR (Damschroder et al., 2009) and will utilize evidence-based implementation strategies (Powell et al., 2012; 2015), as appropriate. The CFIR describes five major domains to consider for implementing a new intervention into routine care: intervention characteristics (e.g., complexity, relative advantage over other options), qualities of the outer setting (e.g., state and local policies, community factors) and inner setting (e.g., program readiness, clinical leadership, and buy-in), individual characteristics of those receiving the facilitation intervention and evidence-based practice (e.g., staff attitudes and beliefs, self-efficacy, social norms and consumer demographic and clinical characteristics), and implementation or facilitation processes (e.g., strategies used, fidelity, and feasibility) and related constructs that provide a pragmatic structure for identifying factors critical to successful implementation of public health-related interventions.

Within the first three months of Phase I, the Collaborative Board will meet for a two-day face-to-face meeting in Albuquerque, NM to begin review and discussion of the information synthesis. The first half-day will consist of introductions, orientation to the CBPR process, and engagement exercises to promote relationship-building and trust among Board Members. There will be brief presentations of the synthesized literature and AI/AN traditional healing. Each presentation will

be followed by interactive activities such as individual writing and sharing; dyadic sharing; small group discussions; and group brainstorming on ways to communicate findings to AI/AN community members and consumers in a clear and engaging manner. One full day of the meeting will consist of a "World Café" method (http://www.theworldcafe.com) whereby each major bulleted topic below will be a small break out group and Collaborative Board members will have a chance to attend each small group to provide input and feedback on the content. One individual remains at the table throughout and serves as a "host" to let others know what ideas have been shared previously so that the new group is able to build upon earlier discussion. Each host presents ideas and group discussion ensues along with voting for top ideas in each area to help guide development of the implementation intervention. Group dialogue about culturally centering MOUD will be audio recorded for use in specific intervention component development later in Phase I.

Specific topics for discussion may include:

- Western and Indigenous Models of Wellness
- Identifying educational components (for consumers and staff)
    - lack of genetic susceptibility data particular to AI/AN people
    - high rates of abstinence
    - cultural identity and spirituality as protective
    - risk factors for SUD
    - MOUD by type of medication and associated treatment outcomes
    - Pain and chronic pain – current and past conceptions
- How to talk about medications for OUD (e.g., as one component of treatment)
    - How does the client use medication(s) for other physical health problems; chronic diseases (e.g., diabetes, hypertension); what did this mean to you, how did that work for you?
    - AI/AN as first pharmacists; that is using medicine/medicinal plants is not new (metaphor, framing)
    - How can AI/AN integrate medications within a traditional spiritual or cultural framework?
    - MOUD to address specific changes in the brain due to opioid use, including reducing craving
    - Medications to facilitate people working towards holistic, integrated wellness (traditional ways, spirituality, religious, mental illness, trauma, fulfilling roles in family, community, Tribe, world)
    - How to talk about pain in terms of traditional AI/AN values, activities, strategies to cope
- How to engage family/community to support the consumer in initiating and adhering to MOUD (e.g., using Community Reinforcement and Family Training [CRAFT] techniques)
- How to engage medical or behavioral health providers who are not supportive of MOUD

Phase II methods will also be discussed and finalized during Months 1-3, including measurement review and feedback and data collection procedures.

11.1.3 Interview Guide Development and Data Collection (approximately Months 4-6)

Following review of materials and identification of knowledge gaps, we will qualitatively examine readiness for MOUD and culturally specific information to guide implementation of MOUD within the four participating sites. In partnership with our Collaborative Board, we will develop interview guides for staff and consumers. The bulleted topics in section 11.1.2 may serve as a starting point to develop the qualitative interview guide. These guides will be used to complete qualitative interviews at two of the four participating sites with staff (i.e., individuals with direct client contact) and consumers (i.e., comprised of individuals currently receiving treatment for OUD or in recovery from OUD). Consumers may also be recruited from other organizations in the AI/AN community in which the site is located. Interviews will be audio recorded and later transcribed for qualitative analysis. The goal of this qualitative data collection effort is to complement information from the literature/resource review and discussion with the Collaborative Board and include specific questions about improving local Tribal community(ies) and program acceptability and cultural congruence of MOUD for staff and consumers.

Procedures

Members of the Lead Team (or the clinical site as preferred) will remotely conduct the qualitative interviews at sites participating in the Phase I qualitative interviews. The site PIs will be asked to identify up to 20 staff members and up to 20 consumers to participate in interviews (see eligibility criteria in section 9.0). Staff and consumers will complete informed consent prior to completing the interview. Interviews are expected to take approximately 45 minutes and participants will be compensated for their time (see section 11.3). It is anticipated that interviews will be conducted individually. Interviews may be conducted by phone/video conference, as needed.

11.1.4 Iterative Development of Culturally Centered MOUD with AI/AN Protocol (approximately Months 6-10)

Based on qualitative data collection and discussions within the Collaborative Board, the Lead Team will draft a preliminary culturally centered MOUD clinical protocol. The drafting process will be iterative and include back and forth feedback between the research team and Collaborative Board. The Collaborative Board may also break into smaller workgroups to focus on specific elements of the protocol (e.g., strategies to prepare the sites for implementation, education on medications, assessing cultural identity salience, connecting traditional AI/AN use of medicine to medications for OUD, shared decision-making elements, holistic conceptualizations of OUD and well-being). Clinical experts in MOUD will review the clinical protocol to ensure fidelity to best practices. Making use of an iterative development process, the Collaborative Board will debrief with regards to acceptability, feasibility, and cultural congruence of the clinical protocol.

11.1.5 Refine Culturally Centered MOUD with AI/AN Protocol (approximately Months 11-12)

The final months of Phase I will be used for refining the intervention based on feedback from all stakeholders. The Collaborative Board will review with specific emphasis on additional cultural centering of MOUD. The implementation intervention will also be reviewed by approximately 3-4 outside (i.e., outside the Collaborative Board) experts in MOUD delivery or AI/AN culture and wellness models for objective feedback selected to compliment characteristics and expertise of the Collaborative Board (e.g., Tribal enrollment, geography). The Lead Team will incorporate final edits. When disagreements arise, we will listen closely to the various perspectives, validate differences, and strive for consensus. If consensus cannot be reached, the Lead Investigators will consult with the co-Investigators to reach a decision and share the process with the Collaborative

Board and sites with an explanation and processing so that we may agree to disagree. In CBPR, 100% consensus is not always attainable but maintaining relationships is of the highest priority.

11.2 Phase II

11.2.1 Screening Visit

If not already available within a participating program, procedures for universal OUD screening will be presented for integration into routine care as part of the implementation intervention. All consumers who meet criteria for OUD within each of the participating sites will be asked to complete screening for the assessment study (following verbal consent), and if eligible, asked if they would like to participate in the assessment portion of the study. If the consumer is eligible and interested, they will complete informed consent procedures and be invited to complete a baseline assessment and three monthly follow-up assessments. Those who screen eligible but are not interested in participating the study will be provided care as usual in accordance with site procedures, including initiation of MOUD as preferred and clinically indicated. Those who screen eligible but are not interested in participating will also be asked about reasons for not wanting to participate in the assessment portion of the study. All consumers with OUD, regardless of their participation in the assessment study, will become part of the site's OUD registry and de-identified data from the EMR (or equivalent) will be used in analysis of primary and secondary outcomes.

OUD Registry

In order for sites to be able to systematically monitor consumers with OUD, regardless of study enrollment, it will be suggested to sites to maintain an OUD registry of all positively screened consumers (i.e., a subset of all consumers). Registries are commonly used as part of integrated care models to monitor patients (Watkins et al., 2003). Once added to the registry, consumers will work with an addiction care coordinator (or other identified staff member) who will confirm the presence of OUD and appropriateness of MOUD. The OUD registry will assist the coordinator (or other identified staff) in tracking consumers with regards to assessment, diagnosis, evaluation, outcome, MOUD or other pharmacotherapy initiation, behavioral intervention, and toxicology reports.

11.2.1.1 Informed Consent Procedures for Participants

Consumers

Study procedures and the potential risks and benefits of participating in the trial will be explained. The designated site staff person will be available to answer questions about the consent form while participants are reviewing it.

Eligible individuals will be provided with an IRB-approved informed consent form. Consent forms will be in compliance with the pertinent sections of 45 CFR 46. Because of the low risks associated with the study, the consent form will be as brief as possible within the constraints of adequate human subjects protections. The consent form will include a description of all significant elements of the study. Staff will be available to answer questions about the consent form while participants are reviewing it. Prior to signing the consent form or giving verbal consent (depending on site-specific procedures), the participant must pass a brief consent assessment to demonstrate adequate comprehension of the study activities. After passing the assessment and signing the consent form or giving verbal consent to participate, participants will be offered a copy of the forms to keep for their records. The informed consent process will take approximately 20-25 minutes to complete.

Staff Participants

Staff with direct consumer contact at each site will be asked to participate in two types of data collection procedures in Phase II: (1) brief survey at six-month intervals and (2) end-of-study qualitative interviews. Surveys of staff will be completed at staff meetings (or equivalent events or on an individual basis as needed). Because the surveys will capture cross sectional organizational level information, no names or participant IDs will be collected, and data will not be linked to individual staff participants over time. A waiver of documentation of informed consent will be requested and staff will read an informational script and check a box agreeing to participate.

At the end of the study, all staff at the participating sites who have direct consumer contact will be asked to participate in a qualitative interview (in person or over the phone). Individuals who are eligible will be provided with an IRB-approved informed consent form. Consent forms will be in compliance with the pertinent sections of 45 CFR 46. Because of the low risks associated with the study, the consent form will be as brief as possible within the constraints of adequate human subjects protections. The consent form will include a description of all significant elements of the study. Research staff will be available to answer questions about the consent form while staff participants are reviewing it. Staff participants will be offered a copy of the forms to keep for their records. The informed consent process will take approximately 10 minutes to complete.

11.2.1.2 HIPAA Authorization and Medical Record Release Forms

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 their IRB(s) or Privacy Boards and obtaining the appropriate approvals or waivers to be in regulatory compliance.

11.2.2 Baseline Visit

Following completion of informed consent, consumer participants will be asked to complete a baseline assessment (see section 12.0 for a list of assessments) which is estimated to take approximately 45 minutes. Ideally, the baseline assessment will occur on the same day as the screening visit and informed consent procedures.

11.2.3 Randomization

Randomization will occur at the program level (4 participating sites) only. Programs will be randomized to receive the implementation intervention either in Step 1 or Step 2. The Data and Statistics Center (DSC) will implement the randomization and will communicate the assignments to the lead investigative team.

11.2.4 Treatment/Intervention

The implementation intervention will take place in the Step 1 sites and will be followed by the Step 2 sites six months later. The implementation intervention will be developed in Year 1 and facilitated by an implementation facilitator(s). The intervention period will be six months.

During the implementation and sustainment stages (Step 1 sites), or the intervention and implementation stages (Step 2 sites) sites may participate in monthly Learning Communities via web-based conferencing. Learning Communities will be developed based on the needs of the clinical sites. The conferences may follow a modified Project ECHO (Komaromy et al, 2016) model based on site preferences and may include “clinical office hours”, brief didactic presentations, case presentations, and education on special populations (e.g., pregnant and postpartum women, co-occurring disorders) and topics (e.g., integrating traditional healing, providing care those who live on and off reservation or travel frequently).

11.2.5 Premature Withdrawal of Participants

All enrolled participants will be followed for the duration of the study unless they withdraw consent, die, or the investigator or sponsor determines that discontinuation is necessary. Reasons for the investigator or sponsor terminating a participant from the study may include, but are not limited to, the participant becoming a threat to self or others, clinical deterioration requiring higher level of care, or lack of funding. Participants who are terminated for clinical reasons will be provided with appropriate referral to higher levels of care. Given that each site will enroll as many eligible and interested consumers as possible during the course of the trial, there will be no specific replacement of participants who withdraw or discontinue early.

Regardless of whether a participant stops receiving MOUD at a participating site, or halts their medical care in general, the participant will be invited to remain in the assessment portion of the study. If the participant is no longer receiving care at the site, research assessments may occur remotely. Assessments may also occur remotely at the discretion of the sites (e.g., depending on COVID-19 protocols); specific procedures will be outlined in site-specific SOPs.

11.2.6 Study Halting Rules

Because this is an implementation study to support the integration of FDA-approved MOUD within primary healthcare or addiction treatment settings, there are no specific criteria to be met that would stop the study early.

11.2.7 Follow-Up

This is an implementation study, following standard clinic procedures. Site staff working on the study (i.e., addiction care coordinator, or equivalent) will make efforts to maintain contact with enrolled participants (as well as all consumers on the OUD registry), including outreach efforts to participants who miss visits.

Participants enrolled in the assessment study will be asked to complete three follow-up research visits at 4 weeks, 8 weeks, and 12 weeks (3 months) after enrollment. At each visit, the addiction care coordinator (or equivalent) will complete assessments using the electronic data capture (EDC) system (see a list of Assessments in **Table 1**), or on paper and later back-entered into the EDC system. Following the visit, the addiction care coordinator (or equivalent) will complete a short checklist to cover key MOUD best practices and note any issues/challenges experienced by the participant. A subset of consumers (approximately 20%) will be randomly selected to also complete a qualitative interview at the 12-week visit. The qualitative interview will take approximately 30 minutes and include questions related to acceptability of services, including treatment for OUD, and appropriateness and relevance of care with respect to culture and perceptions of wellness.

11.3 Reimbursement

11.3.1 Phase I

Consumers will be compensated $40 for qualitative interviews (approximately 40-60 minutes). Staff participants will be compensated $100 for qualitative interviews (approximately 40-60 minutes).

11.3.2 Phase II

Consumer participants will be compensated for each research assessment: $40 for baseline, $25 for assessments at Week 4 and 8 and $40 for Week 12. In addition, a random subset of

participants will be asked to complete qualitative interviews at the Week 12 assessment (approximately 45 minutes) and will receive an additional $30.

Directors will be asked to complete a single quantitative survey one time within the month prior to the beginning of the intervention stage. Staff at each of the participating programs will be asked to complete quantitative surveys (approximately 10 minutes) every six months beginning in the month prior to the beginning of the intervention stage. Staff will receive $10 for each survey they complete. In addition, staff (with direct consumer contact) will be asked to complete a qualitative interview (approximately 45 minutes) at the end of the implementation stage and will receive $100.

12.0 STUDY ASSESSMENTS

The **RE-AIM Model** (Glasgow et al., 1999) was developed as a multi-level framework to guide the evaluation of public health-related implementation. The essential outcomes are: 1) **R**each – proportion of people who are affected by the intervention; 2) **E**ffectiveness – positive and negative individual behavioral, quality of life, satisfaction, and physiologic outcomes of the intervention; 3) **A**doption – proportion and representativeness of participating and non-participating providers/ settings; 4) **I**mplementation – extent to which the intervention is delivered as intended; and 5) **M**aintenance/Sustainability – the extent to which intervention becomes part of routine practice. This model was used to guide the selection of primary and secondary outcomes.

12.1 Table 1: Phase II Assessments

Type	Source	Variable(s)	SCR	BL	WK 4	WK 8	WK 12
Primary (REACH)	Site EMR (or equivalent)	MOUD Initiation (yes or no)	Site Data Extractions [pre-intervention, Month 6, Month 12, Month 18]				
Secondary (EFFECTIVENESS)	Site EMR (or equivalent)	Retention (@ 3 months) ≥ 1 visit per month (yes or no)					
Secondary (ADOPTION)	Site EMR (or equivalent)	MOUD offered (yes or no)					
Secondary (ADOPTION)	Site EMR (or equivalent)	OUD screening (yes or no)					
Descriptive	Site EMR (or equivalent)	Age (yrs), Race, Ethnicity, Sex (where available)					
Exploratory outcome (EFFECTIVENESS)	Site EMR (or equivalent)	Continuation of MOUD for ≥3 months					
Exploratory outcome (EFFECTIVENESS)	Site EMR (or equivalent)	Substance use (urine toxicology results)					
Eligibility	Screening Assessment	Verification the following inclusion criteria: receiving services at participating site; meet criteria for OUD (RODS – brief OUD screen using OUD criteria); self-identify as AI/AN; age 18 or older	X				
Exploratory outcome	PhenX Substance Use Form and Study Urine Toxicology	Self-report lifetime substance use, age at first use, substance use in the last 30 days + tobacco use; single item craving;		X	X	X	X
Exploratory Outcome	Cannabis Assessment	Past-12-month frequency, reasons for use, method of use, weekly frequency of use, daily frequency of use, how marijuana impacts life		X			

Type	Source	Variable(s)	SCR	BL	WK 4	WK 8	WK 12
Exploratory Predictors/Moderators	• Consumer Attitudes and Beliefs about Buprenorphine (Uebelacker et al., 2016) • Consumer MOUD Use and Satisfaction	MOUD attitudes, beliefs, and experiences		X			X
Descriptive	PhenX Demographic Form/ Social Determinants of Health Forms	Age (Yrs), Biological Sex, Gender Identity, Sexual Orientation, Race, Ethnicity, Language, English Proficiency, Tribal Affiliation, learned of MOUD at site		X			
Descriptive	PhenX Demographics Form/Social Determinants of Health Forms	Education, Employment Status, Relationship Status, Zip Code, Health Insurance Coverage, Food Security, Housing Situation, Criteria for CCH Consumer Outcomes Scale		X	X	X	X
Assessments of Safety Events	• Non-Fatal Overdose (NFO) • ED Visits and Hospitalizations • PHQ-9 (NOTE: Also a covariate; see next row)	Number of overdoses in lifetime/since last assessment; substances used during overdose; receipt of Naloxone; Number of visits to the emergency room/number of hospitalizations in past 30 days/since last assessment; number of emergency room visits/hospitalizations related to opioid or other substance use; Depression		X	X	X	X
Mental Health: Covariate/ Exploratory moderator/outcome	• PHQ-9 • GAD-7 • PC-PTSD-5 (5 items) • Adult HOPE Scale (6 items)	Depression; Anxiety; Hopefulness; PTSD		X	X	X	X
Cultural Characteristics: Predictors/ moderators	• Historical Loss Scale (12 items) • Historical Loss Associated Symptoms (12 items) • Native American Spirituality Scale (12 items)	Identity, Connection, Spirituality, Participation		X			X

Type	Source	Variable(s)	SCR	BL	WK 4	WK 8	WK 12
	• American Indian Enculturation Scale (17 items)						
Psychosocial Characteristics: Exploratory Outcomes/Covariates	• Everyday Discrimination Scale (5 items) • PhenX Social Determinants of Health Tool – Disparate Health Care Quality (1 item)	Discrimination		X			X
Consumer Acceptability	• Intervention Feedback Form • Qualitative Interview	Acceptability					X
Study Completion	• NIDA CTN Study Completion Form	Retention					X
Fidelity (IMPLEMENTATION)	Facilitator meetings	Fidelity to the implementation intervention		Intervention Delivery, Implementation			
Site Characteristics: Predictors	Director Survey	Location, size, type		One month Pre-Intervention			
Organizational Characteristics: Predictors/Exploratory Outcomes	Staff Survey	Staff attitudes, social norms, acceptability, readiness		One month prior to start of Intervention, Start of Implementation, End of Implementation			
Staff Acceptability	Qualitative Interview	Acceptability		End of Implementation			

12.2 General Measures

Below is a list of assessments for this protocol. All assessments are reviewed, especially consumer measures, by the Collaborative Board for appropriateness, comprehensiveness, and final approval.

12.2.1 Inclusion/Exclusion – Screening Assessment

This CRF lists each inclusion and exclusion criterion to document eligibility. Only participants who continue to meet study eligibility criteria are allowed to continue with baseline and enrollment process.

The screening assessment will assess consumer participants for inclusion and exclusion criteria that are not assessed through the consent process or confirmed by the site. Specifically, the screener will ask for participant age (to confirm if at least age 18) and race and ethnicity (to confirm self-identification as AI/AN). OUD will be confirmed during the baseline assessment using the Rapid Opioid Dependence Screen (RODS; Wickersham et al., 2015), a shortened screening version of the DSM-5 Checklist. This measure was selected as it can easily be used by community-based sites, including primary care. The screener will also ask consumers whether they plan to move away within three months of screening.

12.2.2 Demographics Form

PhenX Tier 1 demographics and social determinants of health will include: biological sex, gender identity, current educational attainment, current employment status, current relationship status, sexual orientation, zip code, language spoken at home, English proficiency, health insurance

coverage, food security, and current housing situation. Zip code will be collected in order to assess for geographic factors that might influence opioid-related health outcomes, such as local opioid overdose rates, access to health care, and poverty. In addition, specific information on Tribal affiliation will be collected to understand the diversity of the sample and whether it reflects each clinical site and surrounding geographic areas, as well as whether diversity might impact how culture is included or experienced in the context of OUD treatment and services. This form is completed at baseline. Participants will also be asked about how they learned of MOUD being offered at each of the respective sites.

12.2.3 Study Completion Form

This form tracks the participant's status in the study and is completed at the Week 12 visit or once the Week 12 follow-up visit window lapses for participants who do not complete this final follow-up. This form is used in data analyses to address variables such as participant disposition. This form also provides a location for the site PI attestation of review of all study data.

12.3 Measures of Primary and Secondary Outcomes

The primary outcome and multiple secondary outcomes will be captured via each recruitment sites' EMR (or equivalent). Data will be extracted by a designated staff person at each site at six-month intervals. The initial extraction will include EHR data going back to the start of the pre-intervention period. The following outcomes will be extracted from the EMRs (or equivalent):

- **[PRIMARY] MOUD Initiation (binary)**: Number of consumers with OUD initiated onto (received initial prescription) buprenorphine or extended-release naltrexone OR if consumer enrolls in a methadone maintenance program (as documented in the EMR (or equivalent)).
- **[SECONDARY] Number of consumers screened for OUD of the overall number of new consumers** (Implementation; continuous)
- **[SECONDARY] Number of consumers with OUD offered MOUD** (Implementation; continuous)
- **[SECONDARY] Number of consumers screened positive for OUD and retained in care for at least three months** (Clinical; continuous): retention (yes or no) is defined as ≥1 visit per month

12.4 Psychosocial and Cultural Characteristics

- The PHQ-9 (Kroenke et al., 2001) is a 9-item depression scale; it is one of the most validated tools in mental health and used to assist clinicians with diagnosing depression and monitoring treatment response. These 9 items are based directly on the nine diagnostic criteria for major depressive disorder in the DSM-IV.
- The GAD-7 (Spitzer et al., 2006) is a 7-item instrument that uses some of the DSM-V criteria for GAD (General Anxiety Disorder) to identify probable cases of GAD along with measuring anxiety symptom severity. The GAD-7 is modeled after the PHQ9 to be used quickly and effectively within a primary care setting.
- The Adult Hope Scale (Snyder et al., 2007) is a 6-item scale that assesses goal-directed thinking in any given moment or situation.
- The Primary Care PTSD Screen for DSM 5 (PC-PTSD-5) (Prins et al., 2015) is a 5-item screen used to assess for probable posttraumatic stress disorder (PTSD).

- The Everyday Discrimination Scale – Short Version (Sternthal et al., 2011) is a 5-item scale that measures day-to-day experiences with discrimination.
- The PhenX Social Determinants of Health Tool – Disparate Health Care Quality is a single question that assesses whether an individual received sub-standard healthcare because of their race or ethnicity.

The following measures are included to capture culturally specific and relevant characteristics related to the respondents' AI/AN identity, spirituality, and participation in community activities, as well as experiences of historical loss:

- The American Indian Enculturation Scale (Winterowd et al, 2008) is a 17-item self-report assessment capturing involvement/adherence with traditional behavioral and spiritual activities with good reliability (α=.91) (e.g., "attend pow wows or potlatches;" "participate in AI or AN prayers") (Likert Scale 1-7, not at all to a great deal).
- The Historical Loss Scale (Whitbeck et al., 2004) is a 12-item, 6-point scale, self-report measure assessing type of loss (e.g., language, land) and frequency of felt loss for AI/AN adults with excellent reliability (α=.94).
- The Historical Loss-Associated Symptoms is a 12-item measure of potential symptoms associated with experiences of historical loss (α=.89).
- The Native American Spirituality Scale (Greenfield et al., 2015) is 12-item scale to assess the degree to which participants believe in and practice tribe-specific spirituality (α=.79 [Factor 2] to α=.86 [Factor 1]).

12.5 Clinical and Safety Assessments

12.5.1 Safety Events

Given the minimal risk nature of this protocol, the collection and reporting of AEs and SAEs in the data system is not required. Study visits will emphasize OD risk and risk management. Accordingly, only the following Safety Events will be captured: deaths, OD events, suicidal ideation, ED visits and hospitalizations. Study visits will emphasize OD risk and risk management. At each visit, the addiction care coordinator (or designated proxy) will assess for these safety events using the non-fatal overdose, PHQ-9 (suicidal ideation), and ED visits and hospitalization eCRFs. Death events will be captured separately from other primary source documents or reporting. Safety event reporting will be completed according to the reporting definitions and procedures outlined in the protocol and in accordance with the IRB of record and applicable regulatory requirements.

12.5.2 Urine Drug Screen

Urine drug screens (UDS) will be conducted for consumers participating in the assessment portion of the study. UDS will occur at each of the assessment points: baseline and the 4-, 8-, and 12-week follow-up. The CCC will purchase urine drug screens and coordinate shipment of the screens to each of the sites. UDS data will be incorporated into substance use abstinence outcome data. UDS data will be used for research purposes only and will not impact consumers' clinical care, neither will UDS results be reported to consumers' medical providers nor entered into the electronic medical records.

12.5.3 Opioid Use Disorder and Other Substance Use

PhenX Tier 1 (www.phenxtoolkit.org) addiction measures will also be included: lifetime alcohol and other drug use, 30-day alcohol and other drug frequency (plus quantity for alcohol), tobacco use status, and age at first alcohol and other drug use. Finally, the CTN Cannabis Use Assessment will be included to specifically capture marijuana use frequency.

12.5.4 Mental Health Follow-Up Assessment

The Mental Health Follow-Up Assessment form will be triggered and must be completed if a participant endorses suicidality on the PHQ-9 questionnaire. This form is used to document clinician notification and, if performed, suicidal risk assessment by and/or referral to a qualified professional according to the study site SOP. If the participant is at the primary study site (aka on-site), a qualified clinician should be notified and, if indicated, assess the participant's suicidal risk before the participant leaves the hospital or clinic. Regardless of the research encounter setting, all consumers will be given national or local mental health resource referral/contact information (suicide hotline information, etc.) per local site SOPs, when potential suicidal risk is endorsed by the participant on the PHQ-9.

12.6 Intervention Feedback (Acceptability)

Enrolled consumer participants will complete an intervention feedback form at the 12-week follow-up visit, and a subset of consumer participants will complete a brief qualitative interview, also as part of their 12-week follow-up visit. This form will assess basic acceptability of OUD management at the site, including acceptability of MOUD, as applicable.

Qualitative interviews will be conducted with staff at the end of active data collection at the site to assess the culturally centered MOUD implementation intervention.

12.7 Organizational Characteristics

Site characteristics (CFIR domains: inner setting) will be assessed from the Site PI who will complete a survey pre-intervention to include basic information: age of the organization, size (# staff, # consumers), setting (urban, suburban, rural, on tribal lands), distance from health services such as addiction treatment and emergency care, policies for MOUD initiation, use of validated screening tools for mental health and substance misuse, and services provided.

Organizational characteristics (CFIR domains: inner setting and individual) will be assessed from surveys collected from staff at each site to include: staff demographics (race, ethnicity, gender, age in years, professional role, terminal degree, years working for current organization, years providing SUD treatment, knowledge of best practices for SUD treatment, knowledge of traditional AI/AN health practices, attitudes towards MOUD (adapted from Aarons et al., 2012), organizational readiness (ORIC; Shea et al., 2014), intervention acceptability, appropriateness, and feasibility (Weiner et al., 2017), and perceptions of how much the project will improve the health of the community (University of New Mexico survey). .

13.0 TRAINING REQUIREMENTS

13.1 Overall

A comprehensive Training Plan will be developed to incorporate general training, study-specific training, mechanisms for competency assessment as well as a detailed description of training, supervision, and fidelity monitoring procedures. The Investigative Team is responsible for the development of a comprehensive Training Plan, instructional material, and delivery of the training, with the team comprised of the Lead Team (from the Southwest and Greater New York Nodes), CCC, DSC, as well as other participating nodes and subject matter experts, as applicable.

The CTN-0096 study site staff will be trained as specified in the study Training Plan. Training will include HSP and GCP as well as protocol-specific training as needed. For example, assessments, study interventions, safety and safety event reporting, study visits and procedures, data management and QA. The Lead Team is primarily responsible for development and delivery of study-specific training related to the study intervention(s) and procedures. The implementation intervention will be delivered by an implementation facilitator(s) who is/are part of the Lead Team. The CCC is responsible for the development and delivery of non-intervention training, including regulatory safety and safety event reporting, QA and monitoring, etc. The DSC is responsible for training related to data management (DM), the electronic data capture system, and good DM practices. Other parties will contribute as needed based on the subject matter and material to be covered. The various sub-teams will collaborate to deliver quality instructional material designed to prepare research staff to fully perform study procedures based on the assigned research roles and responsibilities.

In addition to general and study-specific training, the Training Plan will include a description of the delivery methods to be used for each training module (e.g., via self-study, online, webcast, or teleconference). Study staff is required to complete institutionally required training per their research site, Institutional Review Board(s)/Privacy Board(s), and authorities with regulatory oversight. 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 Team, 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.

14.0 STATISTICAL DESIGN AND ANALYSES

14.1 General Design

CTN-0096 is a three-year, two-phase implementation intervention study designed to develop and test a culturally centered implementation intervention to integrate MOUD in four sites using a stepped wedge design with two steps. The implementation intervention will be developed during Phase I and testing will occur in Phase II (See **Figure 2**). Sites in Step 1 of Phase II will have six months of pre-intervention, six months of intervention, six months of implementation and six months of sustainment period. Sites in Step 2 will have 12 months of pre-intervention, six months of intervention and six months of implementation period.

14.1.1 Study Hypothesis

The primary objective of Phase I is to develop a culturally centered implementation MOUD intervention using CBPR methods. The main objective of Phase II is to conduct a preliminary evaluation of the implementation intervention in four sites serving AI/AN communities. The primary outcome of the trial is the number of consumers initiated onto MOUD (i.e., one of the three FDA-approved medications) between pre-intervention and implementation measured during Phase II. It is hypothesized that there will be an increase in the number of consumers with OUD initiated onto MOUD from pre-intervention observation to the end of the implementation phase. The overall objectives are to develop the new intervention, and to describe the change in MOUD initiation.

14.1.2 Recruitment and Enrollment

14.1.2.1 Phase I

There will be approximately 8-12 consumer participants and 8-12 staff participants in Phase I to complete qualitative interviews that will be used to inform intervention development. We will work closely with consultants on the Collaborative Board (CB) (approximate 15-20 members). Collaborative Board members will be considered consultants (not research participants); they will guide and assist in the development of the implementation intervention but will not provide research data.

14.1.2.2 Phase II

Consumer participants will be recruited from four study sites. Selected sites will either not have implemented any MOUD but are motivated to do so (i.e., within the next 6-12 months) or are interested in expanding MOUD implementation. Consumers will be receiving services through a qualifying visit (to be determined in collaboration with sites) from the participating sites in order to be included in site level EMR data (or equivalent) or to enroll in the assessment portion of the study. As needed, the Lead Team will discuss strategies with the sites to increase the number of potential consumers with OUD that they might serve at their program (e.g., community outreach, developing linkages/referrals with other community organizations, advertising the availability of MOUD on websites or local professional networks). It is anticipated that word of mouth recruitment will occur organically. Recruitment into the assessment portion of the study will begin following the intervention phase of the study.

Sites will be selected that have the potential (based on current consumer information and community characteristics) to observe approximately 50 AI/AN participants/year who will screen positive for OUD.

14.1.3 Primary and Secondary Outcome Measures

There are no *quantitative* statistical analyses for Phase I since the primary objective is to develop a culturally centered implementation MOUD intervention using CBPR methods. The primary outcome for Phase II is the number of consumers with OUD initiated onto MOUD, and will be compared between the pre-intervention and implementation periods (**Figure 2**). For Step 1 sites, the number of consumers initiated onto MOUD during the sustainment phase (i.e., 6-months after intervention delivery) will be evaluated as a secondary outcome and a signal for sustainability of the intervention.

Other secondary outcomes include:

a) The number of consumers with OUD offered MOUD (implementation outcome);

b) The number of consumers screened for OUD amongst consumers new to the clinic (implementation outcome); and

c) The number of consumers screened with OUD who were retained in care for at least 3 months (clinical outcome).

These outcomes will be measured during the implementation phase and compared to the pre-intervention phase. See section 8.0 for a list of other outcomes.

14.1.4 Randomization and Factors for Stratification

Participants will not be randomized. The sites will be randomly assigned to Step 1 or 2, and stratified by rurality, if possible.

14.2 Statistical Methods for Primary Outcome

PHASE I: Quantitative statistical methods will not be utilized in Phase I.

PHASE II: Phase II will utilize a stepped wedge design where 4 sites will be randomly selected to begin the protocol as illustrated in **Figure 2**. The primary outcome measure is the number of consumers with OUD initiated onto MOUD We postulate a Poisson regression model in which y_{it}~Poisson(λ_{it}) is the number initiated by site i under treatment t, for $i = 1, \dots, 4$ and $t = 0\ (\text{pre} - \text{implementation}, 1 = \text{implementation}$. In this model,

$$\log[\lambda_{it}/(n_i * time_{ij})] = \alpha + \beta * t + \theta_i,$$

where $\theta_i \sim N(0, \sigma^2)$ is a random site effect, n_i is a prior approximation to the size of the site, specifically, to the number of AI/AN patients with OUD that will be seen during a 6-month period at site i, and $time_{ij}$ is the time (in 6-month intervals) spent by site i under treatment t. The term $\lambda_{it}/(n_i * time_{ij})$, which we also call μ_{ij}, is the rate of MOUD initiation per person-time. Note that clinic size is included as an offset term in the Poisson regression model because the four sites are anticipated to vary substantially with respect to size, and the number of MOUD initiations is likely associated with the total number of clinic patients. Interest focuses on β, which is the log of the ratio of the $\mu's$, so that the ratio of the $\mu's$ is $e^{\beta} = \mu_{i1}/\mu_{i0}$, which the model states is constant across all the sites. In other words, e^{β} estimates the rate of MOUD initiation per person-time at a site under the treated condition, divided by the rate per person-time at the same site under the untreated condition. The underlying assumption is that, while these rates may vary across sites (due to the site random effect), the rate ratio does not. This rate ratio is the treatment effect. Note that n_i, being a prior approximation, is the same at a given site under both treatment conditions, while $time_{ij}$ can differ across both sites and treatment conditions.

14.3 Precision Analyses for Primary Outcome

As there is not a formal hypothesis being tested in this trial, and primary interest lies in describing the change in the number of MOUD patients initiating MOUD, we performed precision analyses. The number of sites is limited to 4 due to resource constraints and feasibility, thus we explored the precision of the estimated rate ratio assuming four clinics using preliminary data estimates from the four candidate sites.

14.3.1 Simulation Approach

To predict pre-study the precision with which we expect to know β, we can obtain estimates of some other model parameters (specifically, α and σ^2) by considering data provided from four candidate sites. We regress the candidate site-provided estimate of the number of MOUD initiations in a six-month period using the model $\log[\lambda_{i0}/(n_i * 1)] = \alpha + \theta_i$. Once estimates of $\hat{\alpha}$ and $\widehat{\sigma^2}$ are obtained, we can estimate via simulation an expected confidence interval width for β by assuming that the rate ratio is 4, that is $\beta = \log(4) = 1.39$. These assumptions will allow us to generate simulated Poisson outcomes, and thus perform iterated Poisson regressions as described above, because we know right now not only what the n_i will be, but also what the $time_{it}$ will be.

14.3.1.1 Table 2. MOUD Initiation Estimates Provided by Candidate Sites

Site	Number of AI/AN with MOUD	Number AI/AN Initiated in Six Months
1	3332	4.18
2	73	0.11
3	353	0.63
4	142	0.18

Since the primary outcome is a whole number, we transformed the data by multiplying the number of initiations and the number of months by 100, which should still allow estimation of the α and $var(\theta)$ parameters.

14.3.1.2 Table 3. Transformed Number of AI/AN MOUD Initiations

Site	Number of AI/AN with OUD	Number AI/AN Initiated in 600 Months
1	3332	418
2	73	11
3	353	63
4	142	18

Appendix B describes a small simulation study validating this approach of transforming the number of initiations and the timeframe. From that simulation study, we selected the following values: α = -6.8, and var$(\theta) = 0.02$.

For the precision calculation simulation, comprising 10,000 iterations, Poisson outcomes with means λ_{it} were generated for sites $i = 1, \ldots 4$ and treatment conditions $t = 0\ (pre - implementation, 1 = implementation$ from the model

$$\log\left[\frac{\lambda_{it}}{n_i * time_{it}}\right] = \alpha + \beta t + \theta_i$$

where β = log(4)=1.39, with the n_i values specified in the table above and $time_{it}$ values according to information provided in Table 4.

14.3.1.3 Table 4. Site Stage and Timeline

Site	Period/Stage	Number of Months
1	Pre-intervention	6
	Implementation	6
2	Pre-intervention	6
	Implementation	6
3	Pre-intervention	12
	Implementation	6
4	Pre-intervention	12
	Implementation	6

Note that we assumed sites 1 and 2 were randomly assigned to Step 1, and sites 3 and 4 to sites to Step 2. The value of 4 for the rate ratio was considered clinically meaningful. The four candidate sites all started with approximately 5% initiation rate, and the investigators anticipated the intervention to result in at least a 20% initiation rate during the implementation period.

Once the data were generated, they were fitted to the same Poisson regression model that generated them.

14.3.2 Simulation Results

Table 5 gives mean $\hat{\beta}$ and mean $e^{\hat{\beta}}$(i.e., the estimated rate ratio), the coverage probability of the 95% confidence interval (CI), and the 80th percentiles of the width of the lower limit of the 95% CI, the upper CI limit, and the entire interval. The mean values of $\hat{\beta}$ and $e^{\hat{\beta}}$ are biased upward likely due to asymmetry, but the medians are correct, and the coverage probability of the 95% CI for the rate ratio (RR) is about 99%. If the true parametric values are the same as those simulated, we are unlikely to have a 95% RR CI whose (lower, upper) width exceeds (5.52, 38.52).

14.3.2.1 Table 5: Estimated parameters, coverage probabilities, and 80th percentiles of 95% RR CIs

Mean			Median		Coverage	80th percentile		
$\hat{\beta}$	$e^{\hat{\beta}}$	Var($\hat{\theta}$)	$\hat{\beta}$	$e^{\hat{\beta}}$		CI Lower Limit	CI Upper Limit	CI Width
1.59	5.08	0.03	1.40	4.06	99%	5.52	38.52	44.43

Note: in roughly 0.8% of the simulated outcomes, $e^{\hat{\beta}}$ exceeded 1000. Those cases are ignored in Table 5.

14.4 Secondary Analysis

Like the primary outcome, analyses for secondary outcomes will be descriptive in nature. The outcomes will be summarized using rates, proportions, counts/frequencies and 95% confidence intervals and other statistics such as means, percentiles and standard deviations.

14.5 Significance Testing

Primary outcome analysis will be descriptive in nature; hence there is no anticipated adjustment for multiple testing. Likewise, no multiple comparisons will be adjusted for secondary and exploratory outcomes since these are not part of the study's primary objective.

14.6 Interim Analysis

There are no planned interim analyses.

14.7 Exploratory Analysis

Exploratory analyses will test for differences based on organizational characteristics (inner setting; individual staff and consumers). For Step 1 sites, exploratory analyses will be conducted to compare pre-intervention observations versus sustainment observations.

Other analyses include:

- Exploring organizational predictors of primary and secondary outcomes to include organization characteristics (e.g., rural/reservation vs. urban/suburban settings; program size; co-location of behavioral health or addiction treatment in primary care) and organizational (inner setting) characteristics (e.g., staff attitudes, beliefs, social norms).
- Exploring consumer-level predictors/moderators of primary and secondary outcomes to include sex, psychological distress, cultural identity, spirituality.
- Other diverse outcomes may also be explored including clinical (i.e., mental health, continuation of MOUD) and organizational and staff (i.e., attitudes, intervention acceptability).

Analyses will use similar statistical methods used for primary and secondary outcomes. Additionally, univariate tests like Chi-Square/Fisher exact test, t-test and nonparametric methods will be used where appropriate. Statistical models such as Generalized Linear Models (GLM), Generalized Estimating Equations (GEE) with appropriate distributions and link functions, and Linear Mixed Models (LMM) may be used to evaluate the effect of covariates on the outcome measures where appropriate.

14.8 Qualitative Analysis

All qualitative interviews will follow an interview guide, be digitally recorded and transcribed. Transcribed interviews will be imported into qualitative analysis software (e.g., NVivo or Atlas.ti) for data management and coding. Code books will be developed based on the interview guides with inductive codes added during the coding process. Two research staff will code a small number of interviews to develop reliability; discrepancies will be discussed until consensus is

reached. We will use thematic content analysis to identify common themes and framework analysis to assess differences across sites and respondents. Analysis and interpretation will be conducted in collaboration with the Collaborative Board and clinical sites.

14.9 Missing Data and Dropouts

There are no anticipated missing data for the primary outcome since the data will be extracted from site level data (EMR or equivalent) and the outcome will be assessed after ascertaining that the consumer is eligible for the study. Likewise, there are no anticipated missing data for the implementation secondary outcomes. For the clinical secondary outcomes, we may examine differences between those who induct onto MOUD and those who do not and those who discontinue MOUD before 3 months and those who continue in treatment longer than 3 months.

Several strategies will be implemented to minimize the likelihood and the rate of potential missing data in the proposed study. Timely data entry combined with frequent, planned, and scheduled evaluation of data completeness reports will trigger protocols for tracking and obtaining missing data.

14.10 Demographic and Baseline Characteristics

Baseline demographic and clinical variables will be summarized for participants screening positive for OUD within the clinic (i.e., de-identified site sample), with additional data available for those who enroll into the study and complete assessments. Descriptive summaries of the distribution of continuous baseline variables will be presented with mean and standard deviation. Categorical variables will be summarized in terms of frequencies and percentages.

14.11 Safety Analysis

Although the implementation intervention delivered at the site does not directly involve consumers, there are several safety events that are particularly relevant to this population. These include consumer death, OD events, suicidal ideation, ED visits and hospitalizations collected during Phase II on enrolled participants. The events will be documented and summarized by site.

15.0 REGULATORY COMPLIANCE, REPORTING AND MONITORING

15.1 Statement of Compliance

This trial 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 GCP Guidelines, applicable United States (US) Code of Federal Regulations (CFR), the NIDA Terms and Conditions of Award, and all other applicable state, local, and federal regulatory requirements. The Principal Investigator 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 Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. An Operations Manual will be provided as a reference guide and study QA tool.

15.2 Institutional Review Board Approval

Prior to initiating the study, the lead investigators will obtain written IRB approval to conduct the study from the NYSPI, the IRB of record for the protocol and the IRB providing study oversight in accordance with 45 CFR 46. Each site will determine if they can rely on the NYSPI IRB (and will complete appropriate reliance/authorization agreements) or if they meet exception criteria to NIH's IRB Policy and may require another IRB's approval (e.g., sites that are part of sovereign Tribal nations or sites the must obtain approval from a Tribal Council or Indian Health Board), or a regional IRB based on site policies and preferences. 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. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. 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 investigator 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.

15.3 Informed Consent

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. Informed consent continues throughout the individual's study participation. The informed consent form will include all of the required elements of informed consent and may contain additional relevant consent elements and NIDA CCTN specific additional elements. Each study site must have the study informed consent forms approved by the Single IRB (sIRB) or the site regional IRB. Prior to initial submission to the IRB and with each subsequent consent revision, the consent form(s) must be sent to the CCC and the Lead Team to confirm that each consent form contains the required elements of informed consent as delineated in 21 CFR 50.25(a) and CFR 46.116(c), as well as pertinent additional elements detailed in 21 CFR 50.25(b) and 45 CFR 46.116(c) and any applicable CCTN requirements. Every study participant is required to sign a valid, IRB-approved current version of the study informed consent form prior to the initiation of any study related procedures unless determined otherwise by the site regional IRB. The site must maintain the original signed informed consent and verbal consent tracking log for every participant (unless determined otherwise by the site regional IRB) in a locked, secure location that is in compliance

with all applicable IRB and institutional policies and that is accessible to the study monitors. Every study participant must be given a copy of the signed consent form.

During the informed consent process, research staff will explain the study to the potential participant and offer the potential participant a copy of the consent form to read and keep for reference. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and their rights as research participants. Extensive discussion of risks and possible benefits will be provided to the participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to agreeing to participate in the study. The participants should have the opportunity to discuss the study with their family and close friends or think about it prior to agreeing to participate. If the participant is interested in participating in the study, a qualified staff member will review each section of the IRB-approved informed consent form in detail and answer any questions the participant may pose. The participant, or participant's legally authorized representative, will consent by completing and passing the consent quiz, signing and dating the consent document (or indicate agreement to participate as appropriate if documentation of consent is approved by the IRB in specific circumstances). The person obtaining consent and a witness, if required by the IRB of record, will also sign and date the consent document. It is strongly recommended that another research staff member review the consent after it is signed to ensure that the consent is properly executed and complete. Staff members delegated by the PI to obtain informed consent must be listed on the Delegation of Responsibility and Staff Signature Log and must be approved by the IRB, if required. All persons obtaining consent must have completed appropriate GCP and HSP training, as mandated by NIDA standard operating procedures.

The informed consent form must 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. A copy of the informed consent will be given to a prospective participant to review during the consent process and to keep for reference. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. 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 QA review and regulatory compliance.

15.3.1 Additional Procedures for Screening Verbal Consent

We will request a waiver of written informed consent from the IRB of record for this study for screening (Phase II consumers) and staff surveys, unless determined otherwise by the site regional IRB (e.g., waiver of written informed consent could be approved for screening and verbal consent procedures). In accordance with applicable federal regulations (45 CFR 46.116(f)), these portions of the study protocol meet 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.

The study does not preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective. It is in conformance with 42 CFR 2.52, which allows for research-related provisions with regard to the disclosure of SUD patient identifying information in the absence of the informed consent process and HIPAA authorization.

15.4 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 the IRB of record (as applicable) for further review.

15.5 Participant and Data Confidentiality

Participant confidentiality and privacy are strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) 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.

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), and regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. 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 Records Retention and Requirements (see below).

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.

15.5.1 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. The CoC allows the investigator and others who have access to research records to permanently refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level, excepting certain circumstances.

By protecting researchers and institutions from being compelled to disclose information that would identify research participants, the Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

15.5.2 Health Information Portability Accountability Act (HIPAA)

Study sites will be required by their institutions to obtain authorization from participants for use of protected health information. Sites will be responsible for communicating with the sIRB, Privacy Boards of record, or regional IRB (if applicable), and obtain 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.

15.6 Investigator Assurances

Each site must file (or have previously filed) a Federal Wide Assurance (FWA) with the HHS 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, 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 principal investigator at each study site will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

15.6.1 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.

15.7 Clinical Monitoring

Investigators will host periodic visits by NIDA contract Clinical Research Associates (CRAs) 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 CRAs will audit, at mutually agreed upon times, regulatory documents, case report forms (CRFs), informed consent forms and corresponding source documents for each participant. CRAs will have the opportunity and ability to review any study-associated document or file.

NIDA-contracted CRAs 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 principal investigator 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 party(ies) will provide site management for each site during the trial. Node QA staff or other designated party(ies) 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.

15.8 Inclusion of Women and Minorities

The study sites should aim and take steps to enroll a diverse study population. In this study, all enrolled consumer participants will identify as American Indian or Alaska Native (mixed heritage will be included). The staff participants may be of any ethnic heritage. However, if difficulty is encountered in recruiting an adequate number of participants or participants with diverse characteristics (e.g., women), the difficulties involved in recruitment will be discussed within the Collaborative Board and on national conference calls and/or face-to-face meetings as needed.

15.9 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.

If a participant in the study becomes a prisoner during the course of the study, and the relevant research proposal was not reviewed and approved by the IRB in accordance with the requirements for research involving prisoners under Subpart C of 45 CFR 46, the investigator must promptly notify the IRB. All research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated participant must be suspended immediately. The lone exception to this regulation is if the investigator asserts that it is in the best interests of the prisoner-participant to remain in the study while incarcerated. The investigator must promptly notify the IRB of this occurrence.

15.10 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and 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.

15.11 Records Retention and Requirements

Research records for all study participants (e.g., case report forms, source documents, signed consent forms, audio and video recordings, and regulatory files) are to 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.

15.12 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. Safety reporting (e.g., safety reporting) will occur as previously described. At the completion of the trial, the Lead Investigator will provide a final report to the Sponsor.

15.13 Audits

The Sponsor has an obligation to ensure that this trial is conducted according to good research practice guidelines and may perform QA audits for protocol compliance. The Lead Investigators and authorized staff from the Southwest Node and Greater New York 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 Institutional Review Board of record may inspect research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety.

15.14 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 case report forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Institutional Review Board 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 QA 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. All study related documents must be made available for source data review and source data verification.

15.15 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 QA 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 Team and the CCC with overall approval by the IRB of record as needed. 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 and submitted to the Lead Team and CCC via a Protocol Deviation Tracking Log. This log will document a description of the deviation, how it occurred, the corrective action taken to resolve the specific deviation, as well as a description of the plan implemented to prevent future occurrences of similar deviations. The CCC, DSC and the Lead Investigator must be contacted immediately if an unqualified or ineligible participant is randomized into the study.

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.

15.16 Safety Monitoring

Because this is a minimal risk study with no pharmacological intervention, Adverse and Serious Adverse Events (SAEs) are not anticipated for this study. Death, OD events, suicidal ideation, ED visits and hospitalizations will be considered safety events and captured on separate CRFs. Each of the sites has established practices for managing medical and psychiatric emergencies, and the study staff will continue to utilize these procedures. Treatment providers at each site will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

15.16.1 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 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).

15.16.2 Adverse Events (AEs) & Serious Adverse Events (SAEs)

Given the minimal risk nature of this protocol, the collection and reporting of AEs and SAEs in the data system is not required.

15.16.3 Safety Events

Because of the minimal risk nature of this protocol, only the following Safety Events will be captured: deaths, OD events, suicidal ideation, ED visits and hospitalizations among consumer participants in Phase II. These events will be captured on study-specific CRFs, not on AE/SAE

forms, from baseline through week 12. The source of the information on these events may be the EMR or self-report (in the case of non-fatal ODs and suicidal ideation that does not result in death). Research staff may also utilize other methods to confirm these outcomes if the consumer participant does not return to the research site. For confirmed death events, sites will report in eClinical within 24 hours of awareness of the event. For overdose events and suicidal ideation identified at scheduled study visits, sites will report in eClinical within 48 hours of the event.

16.0 DATA MANAGEMENT

16.1 Design and Development

This protocol will utilize a centralized Data and Statistics Center (DSC). There are two distinct types of data sources for this study. The primary and key secondary outcomes will be based on data extracted from the site EMR (or equivalent) and transmitted to the DSC. The second data stream involves survey and assessment data collected solely for the purposes of this study (i.e., secondary data). For the latter data source, the DSC will be responsible for development of the electronic case report forms (eCRFs), development and validation of the clinical study database, ensuring data integrity, and training site and participating node staff on applicable data management procedures. Advantage eClinical, a web-based distributed data entry system, will be implemented. This system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld.

In addition, we will utilize EMR (or equivalent) data from each of the clinical sites to document consumer flow, screening for SUD (especially OUD), prescriptions for MOUD, retention, etc. Staff from the DSC will work in close collaboration with programming staff from each EMR source (since some sites may use the same EMR source) to determine the specific measures to be abstracted, with guidance from the lead investigative team, and harmonize data to prepare for combining all datasets into the official study version. The repository established to house the data from both data sources for this study will be developed by the DSC to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld, and confidentiality of data is maintained.

The remainder of this section provides an overview of the data management plan associated with this protocol.

16.2 Site Responsibilities

The data management responsibilities of each individual site for the survey and assessment data collected in Advantage eClinical will be specified by the DSC and outlined in the corresponding Advantage eClinical User's Guide and CRF Manual.

Each clinical site must provide IT technical staff, with familiarity and access to site level data (EMR or equivalent), who can work with the DSC in extracting data at predetermined intervals, transmitting the data to the DSC in a secure fashion agreed upon by both parties, and addressing any data quality issues identified by the DSC during back-end data cleaning. Ideally, the clinical site programmer(s) will also perform certain data quality measures prior to transferring to the DSC. In addition, if patient-level information will be provided by a site, the clinical site staff/programmers will work with appropriate staff from the DSC to ensure that data can be linked on a record-by-record basis with the secondary data from Advantage eClinical.

16.3 Data Center Responsibilities

The DSC will 1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, 2) provide final Case Report Forms (CRFs) and electronic CRFs (eCRFs) for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) prepare instructions for use of Advantage eClinical and for completion of CRFs/eCRFs, 5) conduct ongoing data validation and cleaning activities on study data from all participating sites, 6) perform data validation and cleaning activities prior to any interim analyses and prior to study database lock.

In addition, the DSC will work with all of the other entities to obtain the appropriate agreements for utilizing the EMR data or equivalent (i.e., Data Transfer Agreements or Data Use Agreements, as necessary). These parties will also work together to determine the best procedures for the data

transfers, such as uploading data directly into an electronic data capture system. The DSC will also ensure that all parties involved in these data transfer/uploads and the repository will be authorized, validated users and that no PHI (protected health information) or PII (potentially identifying information) are shared. The Emmes Company has provided more than 60 integrations successfully protecting both PHI and PII. Those integrations involved data transfer from numerous entities including Federal agencies, universities, repositories and labs.

16.4 Data Collection and Entry

Data (i.e., surveys and other assessments) will be collected will be obtained at the study sites on source documents (using paper and pen) and entered by the site into eCRFs in Advantage eClinical, or will be collected via direct entry into the eCRF. In the event that Advantage eClinical is not available, the DSC will provide the sites with CRF paper source documents and completion instructions. Data entry into Advantage eClinical should be completed according to the instructions provided and project specific training and guidelines established by DSC. Data entry into eCRFs shall be performed by authorized individuals. The investigator is responsible for maintaining accurate, complete and up-to-date records, and for ensuring the completion of the eCRFs for each research participant. Selected eCRFs may also require the investigator's electronic signature.

The process for site level data extraction (i.e., secondary data) from EMRs will be developed once the sites are identified and it has been agreed upon what types of data the sites are able to extract.

16.5 Data Editing

Data collected solely for the purposes of this study (surveys and study assessments) will be entered into the DSC automated data acquisition and management system (Advantage eClinical). eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and forms are available to sites at all times in Advantage eClinical. These reports will be monitored regularly by the DSC. In addition, the DSC will identify inconsistencies within eCRFs and between eCRFs and post data clarification requests or queries in Advantage eClinical on a scheduled basis. Sites will resolve data inconsistencies and errors and enter all corrections and changes into Advantage eClinical.

The CCC will conduct regular monitoring visits, during which audits comparing source documents to the data entered on the eCRF will be performed. Any discrepancies identified between the source document and the eCRF will be corrected by the site.

Trial progress and data status reports, which provide information on items such as recruitment, regulatory status, and data quality, will be generated daily and posted to a secure website. These reports are available to the site staff, the local node staff, the lead node, the coordinating centers, and NIDA CCTN to monitor study progress overall and at each individual participating site.

The EMR-extracted data will initially be transferred to the DSC, who will then evaluate the quality and consistency of the data and provide feedback to the appropriate source. If necessary, repeat transfers may be required in order to meet deliverable timelines, such as in preparation for an interim DSMB review. The DSC will not make edits to the data received, per Good Clinical Data Management Practices, but will request that the data originator address any concerns and make updates as necessary.

16.6 Data Transfer/Lock

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DSC. This will not include anyone's contact or

identifying information, other than date of birth and zip code, for participants consented to be enrolled and followed-up during Phase II. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by DSC staff will be secured and password protected.

Study data from all data streams will be combined in a repository and those data will be transmitted by the DSC to the NIDA central data repository. The DSC will conduct final data cleaning activities and “lock” the study database from further modification. The final raw analysis dataset will be transferred to the Lead Investigator or designee and to NIDA, as requested, with approval by Tribal governing bodies, for storage and archiving. Datasets will be made available to the public with approval from relevant IRBs and Tribal governing bodies. A standalone Data Sharing Plan, specific to each site and with approval from Tribal governing bodies as needed, will describe agreements for data ownership, sharing, transmission, and publication processes.

16.7 Data Training

The training plan for site staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of Advantage eClinical.

16.8 Data Quality Assurance

To address the issue of data entry quality, the DSC will follow a standard data monitoring plan. An acceptable quality level prior to study lock or closeout will be established as a part of the data management plan. Data quality summaries will be made available during the course of the protocol.

17.0 PUBLIC ACCESS AND DATA SHARING PLAN

To the extent possible, this study will comply with the NIH Data Sharing Policy and Implementation Guidance (https://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm) and the HEAL Public Access and Data Sharing Policy (https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative/research/heal-public-access-data-sharing-policy). Investigators will also register and report results of the trial in ClinicalTrials.gov, consistent with the requirements of the Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration (https://grants.nih.gov/policy/clinical-trials/reporting/understanding/nih-policy.htm).

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, and all publications will also be deposited in PubMed Central http://www.pubmedcentral.nih.gov/ per NIH Policy (http://publicaccess.nih.gov/).

The plan for data sharing will be detailed in a standalone Data Sharing Plan, specific to each site and with approval from Tribal governing bodies, as needed, which will describe agreements for data ownership, sharing, transmission, and publication processes.

18.0 PROTOCOL SIGNATURE PAGE

SPONSOR'S REPRESENTATIVE (CCTN SCIENTIFIC OFFICER OR DESIGNEE)

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 2.0 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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20.0 APPENDIX A: DATA AND SAFETY MONITORING PLAN

20.1 Brief Study Overview

Opioid-related mortality is magnified among the U.S. American Indian/Alaska Native (AI/AN) population. Although FDA-approved medications for opioid use disorder (OUD) are first line treatments, uptake of these medications for OUD has been limited among rural and urban Tribal communities due to structural, psychosocial, cultural, and spiritual reasons. The proposed study seeks to develop and test a culturally centered program-level implementation intervention to support the integration of medications for OUD (MOUD) with AI/AN consumers in healthcare and addiction specialty settings. The study will consist of two phases over three years. In Phase I, using CBPR methods, in partnership with a Collaborative Board and drawing from cultural adaptation, implementation, and coordinated care models, we will develop a culturally centered implementation intervention. In Phase II, we will test the implementation intervention in four sites utilizing a stepped wedge design (2 steps, 2 clinics per step). The primary outcome is the number of patients who initiate onto MOUD in the 6 months after intervention delivery (compared to the 6 months before intervention delivery); secondary outcomes include the number of: patients screened for OUD, patients with OUD offered MOUD, and patients with OUD retained in treatment for 3 months. Site/Organizational characteristics will be explored for associations with outcome.

20.2 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 medical clinicians to assess, report, and monitor safety events.

This study will collect safety events, including deaths, overdose (OD) events, suicidal ideation, ED visits and hospitalizations among consumer participants in Phase II. These events will be captured on study-specific CRFs, rather than on AE/SAE forms, from baseline through week 12. The source of the information on these events may be the EMR or self-report (in the case of non-fatal overdoses and suicidal ideation that does not result in death). Research staff may also utilize other methods to confirm these outcomes if the consumer participant does not return to the research site. For confirmed death events, sites will report in eClinical within 24 hours of awareness of the event. For overdose events and suicidal ideation identified at scheduled study visits, sites will report in eClinical within 48 hours of the event.

All protocol specified safety events occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the Protocol.

The occurrence of safety events will be assessed at each study visit during the study.

B. CCC Medical Monitor

The NIDA CTN Clinical Coordinating Center's (CCC) Safety Monitor/Medical Monitor or designee is responsible for reviewing all safety events reported. All death events will be reviewed at the time that they are reported in the EDC. Other safety events will be monitored on a weekly basis. The Safety Monitor/Medical Monitor or designee will also indicate concurrence or not with the details of the report provided by the site PI. Where further information is needed, the Safety Monitor/Medical Monitor or designee will discuss the event with the site staff. Reviews of safety events by the CCC Safety Monitor/Medical Monitor or designee will be documented in the Advantage eClinical data system and will be a part of the safety database.

C. Data and Safety Monitoring Board (DSMB)

The NIDA CTN DSMB affiliated with this trial will be responsible for conducting periodic reviews of accumulating safety, trial performance, and outcome data. Reports will be generated and presented for Data and Safety Monitoring Board (DSMB) meetings. The DSMB will receive listings of safety events at a frequency requested by the DSMB, but at least annually. The DSMB will make recommendations to NIDA CCTN as to whether there is sufficient support for continuation of the trial, evidence that study procedures should be changed, or evidence that the trial (or a specific site) should be halted for reasons relating to safety of the study participants 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 Monitoring

The monitoring of the study site(s) will be conducted on a regular basis using a combination of NIDA CCTN CCC monitors and the local Node QA Monitors (if applicable). Investigators will host periodic visits for the monitors. The purpose of these visits is to assess compliance with the protocol, GCP requirements, and other applicable regulatory requirements, as well as to document the integrity of the trial progress. The investigative site will provide direct access to all trial related sites (e.g., pharmacy, research office), source data/documentation, and reports for the purpose of monitoring and auditing by the monitors, as well as for inspection by local and regulatory authorities. Areas of particular concern will be the review of inclusion/exclusion criteria, participant Informed Consent Forms, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, and Principal Investigator supervision and involvement in the trial. The monitors will interact with the site staff to identify issues and re-train the site as needed to enhance research quality.

Site Visit Reports will be prepared by the NIDA CCC monitors following each site visit. These reports will be sent to the site Principal Investigator, the study Lead Investigator and NIDA CCTN and other parties as designated.

Local Node QA site visit reports will be prepared following each site visit, as applicable. These reports are sent to those entities required of them by the Lead Investigative team, generally including the Lead Investigator, site Principal Investigator, Node PI and a CCC representative, usually the clinical study manager for the study.

E. Management of Risks to Participants

Confidentiality

Confidentiality of participant records 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 and securely stored 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

The consent form will specifically state the types of information that are required for reporting and that the information will be reported as required. These include suspected or known sexual or physical abuse of a child or elders, or threatened violence to self and/or others.

Participant Protection

Individuals who experience a safety event that compromises safe participation in a study will be discontinued from further assessment and provided referrals for other treatment or to specialized care, as needed.

Pregnancy

As there is no medication intervention being tested, pregnancy will not be followed within the context of this study. Each site will manage pregnancy per standard care.

Study Specific Risks

There are no specific risks to participation in this implementation intervention study, other than those standard to minimal risk research (e.g., breach of confidentiality).

20.3 Data Management Procedures

This protocol will utilize a centralized Data and Statistics Center (DSC). A web-based distributed data entry model will be implemented for data that is collected solely for the purpose of this study. This electronic data capture system (Advantage eClinical) will be developed to ensure that guidelines and regulations surrounding the use of computerized systems in clinical trials are upheld.

The DSC will also collaborate with each site to receive reports from the EMR (or equivalent).

20.4 Data and Statistics Center Responsibilities

The DSC will: 1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, 2) provide source documents and electronic Case Report Forms (eCRFs) for the collection of all assessment data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) prepare instructions for the use of Advantage eClinical and for the completion of eCRFs, 5) conduct ongoing monitoring activities on study data collected from all participating sites, 6) perform data cleaning activities prior to the final study database lock, and 7) perform harmonization for the EMR-extracted data in collaboration with the lead investigative team and programming staff from the sites.

20.5 Data Collection and Entry

Assessment-based data will be collected at the study sites on source documents and entered by the site into eCRFs in Advantage eClinical or will be collected via direct entry into the eCRF. In the event that Advantage eClinical is not available, the DSC will provide the sites with a final set of guided source documents and completion instructions. Data will be entered into Advantage eClinical in accordance with the instructions provided during protocol-specific training and guidelines established by the DSC. Data entry into the eCRFs is performed by authorized individuals. Selected source documents and eCRFs may also require the investigator's signature (wet or electronic). In some situations, data collected on source documents will not be entered into Advantage eClinical, but when it is entered, it will follow the guidelines stated above.

The Principal Investigator at the site is responsible for maintaining accurate, complete and up-to-date research records. In addition, the Principal investigator is responsible for ensuring the timely completion of eCRFs for each research participant.

EMR data from each clinical site will be extracted "onsite" and transferred in a secure fashion to the DSC.

20.6 Data Monitoring, Cleaning and Editing

For primary data, eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and missing forms are available to sites at all times in

Advantage eClinical. These reports will be monitored regularly by the DSC. In addition, the DSC will identify inconsistencies within eCRFs and between eCRFs and post queries in Advantage eClinical on a scheduled basis. Sites will resolve data queries by entering all corrections and changes directly into Advantage eClinical or verifying the data are correct as is.

As described above, the CCC will conduct regular monitoring visits, during which audits comparing source documents to the data entered on the eCRF will be performed. Any discrepancies identified between the source document and the eCRF will be corrected by the site.

EMR data (or equivalent) will be transferred to the DSC, who will then evaluate the quality and consistency of the data and provide feedback to the appropriate source. If necessary, repeat transfers may be required in order to meet deliverable timelines, such as in preparation for an interim DSMB review. The DSC will not make edits to the data received, per Good Clinical Data Management Practices, but will request that the data originator address any concerns and make updates as necessary. Some examples of data issues requiring site programming/technical staff to make updates include formatting or structural errors, inconsistent data and inappropriate data such as PHI or any prohibited by the appropriate Data Use Agreement (DUA). Ideally, some level of quality control will be implemented by the site prior to transmission to the DSC for the EMR data (or equivalent). Metrics will be developed to assess data quality in collaboration with the lead investigative team. While every effort will be made to identify these metrics *a priori*, EMR systems are dynamic and new issues arise regularly, thus the plan for evaluating data quality and the specific metrics needs to be fluid and responsive as well.

Trial progress and data status reports, which provide information on items such as recruitment, availability of primary outcome, attendance at follow-up visits, regulatory status, and data quality, will be generated daily and posted to a secure website. These reports are available to the site staff, the local Node staff, the Lead investigators (LIs), the coordinating centers, and NIDA CCTN, to monitor each sites' progress on the study.

20.7 Database Lock and Transfer

Research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DSC. Individuals and their research data will be identified by a unique study identification number; further, some identifiable data, such as date of birth, may be collected in eClinical. The study data entry and study management systems used by clinical sites and by DSC staff will be secured and password protected.

At the conclusion of data collection for the study, the DSC will perform final data cleaning activities and will "lock" the study database from further modification. The final raw datasets will be transferred to the Lead Investigator or designee. De-identified versions of the primary datasets will also be provided to the NIDA CCTN-designated party for storage and archiving, if required by CCTN. Datasets will be made available to the public with approval from relevant IRBs and Tribal governing bodies. A standalone Data Sharing Plan, specific to each site and with approval from Tribal governing bodies as needed, will describe agreements for data ownership, sharing, transmission, and publication processes.

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

21.0 APPENDIX B: SIMULATION DETAILS FOR PRECISION ANALYSES

A complication with the initial data provided by the candidate sites is that the estimated numbers initiated in six months contain decimals but with approximately equally-sized time periods. A potential solution to this problem is to multiply all the decimal values by, say 100, and then use 100 as the time part of the offset. This should allow estimation of the α and $var(\theta)$ parameters, because of the way the offset works[1]. To test this idea, we did 5 different regressions, each time multiplying the number of AI/AN with OUD initiated onto MOUD by a different value, denoted by "MPY" and setting the corresponding time to MPY. Results for estimates of $var(\theta)$ and α are shown in Tables B.1 and B.2, respectively.

Table B.1: Estimated values of $var(\theta)$ using different MPY values

MPY	Estimate	Standard Error
100	0.01217	0.01953
1000	0.02038	0.01586
10000	0.02081	0.01487
100000	0.02084	0.01476
1000000	0.02085	0.01475

Table B.2: Estimated values of α using different MPY values

MPY	Estimate	Standard Error
100	-6.5742	0.09633
1000	-6.5464	0.07750
10000	-6.5447	0.07283
100000	-6.5445	0.07226
1000000	-6.5445	0.07220

There are slight differences between the MPY estimates, however we assume these are a result of the numerical methods used in GLIMMIX, rather than being bona fide results of the values of

MPY. These results suggest that α = -6.8, $var(\theta)$ = 0.02 are reasonable estimates and were used in the simulations for the precision analyses.