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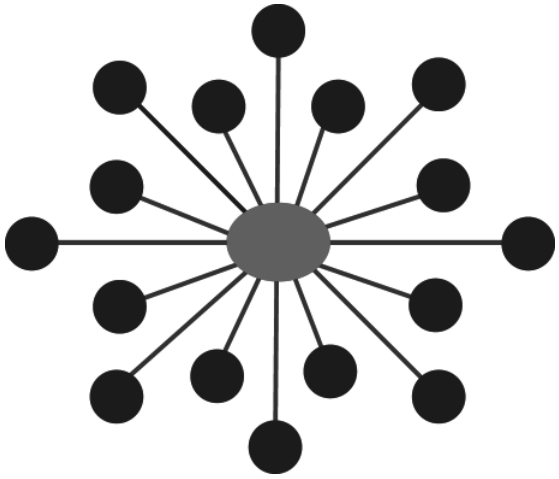

NIDA CTN Protocol 0084-A2

Harnessing Digital Health to Understand Clinical Trajectories of Opioid Use Disorder (D-TECT)

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AMRS	Addiction Medicine Recovery Services
API	Application Programming Interface
CDC	Center for Disease Control
CCTN	Center for Clinical Trials Network
CLIA	Clinical Laboratory Improvement Amendments
CoC	Certificate of Confidentiality
CFR	Code of Federal Regulations
CRF	Case Report Form
CTN	Clinical Trials Network
DM	Data Manager/Management
DSC	Data and Statistics Center
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Forms
EHR	Electronic Health Record
EMA	Ecological Momentary Assessment
ERC	Ethics Review Committee
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
GPS	Global Positioning System

HEAL	Helping to End Addiction Long-term
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HSP	Human Subjects Protection
ICH	International Council for Harmonization
IRB	Institutional Review Board
KPNC	Kaiser Permanente System in Northern California
LI	Lead Investigator
LN	Lead Node
MAR	Missing at random
MCAR	Missing completely at random
MNAR	Missing not at random
MOP	Manual of Procedures
MOUD	Medications for Opioid Use Disorder
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
OHRP	Office for Human Research Protection
OUD	Opioid Use Disorder
PhenX	Phenotypic traits and Environmental eXposures
PI	Principal Investigator
PM	Project Manager
QA	Quality Assurance
RA	Research Assistant

RC	Research Coordinator
SAE	Serious Adverse Event
NetSCID-5	Web-based Structured Clinical Interview for DSM-5
SUD	Substance Use Disorder
UDS	Urine Drug Screen
UP	Unanticipated Problems

2.0 STUDY SYNOPSIS

Across the U.S., the prevalence of opioid use disorder (OUD) and the rates of opioid overdoses have risen precipitously in recent years. Drug overdose is being called a “modern plague” (Katz, 2017) and is now the leading cause of death of Americans under age 50, having surpassed peak death rates from gun violence, HIV, and car crashes (Centers for Disease Control and Prevention (CDC), 2018; Katz, 2017). This dramatic spike in OUD has also been accompanied by marked increases in injection-related infections (including infective endocarditis and Hepatitis C) (Centers for Disease Control and Prevention (CDC), 2016, 2017; Hartman et al., 2016; Keeshin & Feinberg, 2016), babies born with Neonatal Opioid Withdrawal Syndrome (Patrick, Davis, Lehmann, & Cooper, 2015) and healthcare and criminal justice costs (Rhyan, 2017).

Several effective medication-assisted treatments for OUDs exist. Treatment models for OUDs that include buprenorphine medication are among the most effective treatment models. Buprenorphine treatment for OUD has been shown to greatly increase opioid abstinence, reduce HIV/infectious disease risk behavior, and criminality. Greater retention in such treatment models are associated with the most positive treatment outcomes (Connock et al., 2007; Johnson, Jaffe, & Fudala, 1992; Ling et al., 1998; Sordo et al., 2017a). However, given the chronic relapsing nature of the disease of addiction, many individuals continue to engage in opioid use during treatment. Further, many individuals who enter buprenorphine treatment do not consistently take their medication or remain engaged in treatment – typically resulting in continued opioid use (which is accompanied by risk of overdose) (Fiellin et al., 2008; Schuman-Olivier, Weiss, Hoeppner, Borodovsky, & Albanese, 2014). Although many factors (e.g., stress, mental health comorbidities, and continued exposure to high risk social networks or contexts) have been shown to predict non-adherence in substance use disorder treatment (Simon et al., 2017; Weinstein et al., 2017), most studies have examined a small set of potential moderators or mediators of outcomes in treatment for OUD and may lead to over-simplified accounts of treatment non-adherence.

More frequent and longer assessment of moderators, mediators, and outcome(s) are necessary to elucidate the temporal dynamics between changes in specific mechanisms and treatment non-adherence behavior (Collins & Graham, 2002). Examining a broad array of factors impacting treatment non-adherence at multiple levels of analysis will enable a more comprehensive picture and will increase our ability to develop more impactful interventions for OUD.

Advances in **digital technologies and data analytics** have created new opportunities to assess and modify health behavior and thus accelerate the ability of science to understand and contribute to improved health behavior and health outcomes. Given the ubiquity of access to digital technologies worldwide, digital tools allow for the examination of health behavior and clinical trajectories within-individuals through intensive collection of individual-level, real-time data collected via surveys on mobile device (referred to as Ecological Momentary Assessment [EMA]), wearable sensors (on smartphones and/or smartwatches), and mapping digital footprints. Digitally-derived data allow for the development of dynamic models of health behavior to understand behavior in real-time and in response to changing environmental, social, physiological, and intrapersonal factors (Naslund et al., 2017; Spruijt-Metz, 2014). As applied to persons with OUD, digital data that offers ongoing assessment of behavior as individuals live their daily lives can help us better understand the trajectory of clinically important behaviors (e.g., treatment retention; medication adherence over time) and identify fluctuating contextual factors that greatly influence such behaviors, (e.g., patterns leading to relapse or treatment dropout).

Parent Study

This study is an ancillary study to CTN 0084 “Establishing an Opioid Registry Across Diverse Health Systems” (PI: Cynthia Campbell). An aim of CTN 0084 focuses on the use of EHR data from several health systems to examine the relationship between different lengths of buprenorphine retention and mortality. The optimal duration of buprenorphine treatment to reduce the risk of relapse, overdose, and mortality outcomes is unknown, although generally a longer length of treatment is related to better opioid use outcomes and lower risk of mortality (Dupouy et al., 2017; Sordo et al., 2017b; Weiss & Rao, 2017). However, retention in treatment remains a well-documented challenge and factors such as relapse, other substance use, inability to adhere to program stipulations, loss of insurance, cost, patient preference, provider practice, or health system policies can be related to discontinuation. CTN 0084 examines the distribution of buprenorphine retention, associated patient and health system characteristics, and rates of mortality, providing a high level view of this problem. This ancillary study complements the parent study by offering a “deep dive” into key factors associated with treatment retention (examining EHR data complemented by digitally-derived data) through data collected in real-time from a subset of patients in buprenorphine treatment for OUD as they live their daily lives. This ancillary study is a pilot, observational study and is not powered to test specific hypotheses.

2.1 Study Objectives

The primary objective of this study is to evaluate the feasibility of utilizing digital health technology (EMA and digital sensing) continuously over a 12-week period and collecting social media data.

The secondary objective is to examine the utility of EMA, digital sensing, and social media data (separately and compared to one another) in predicting OUD treatment retention, buprenorphine medication adherence (as captured in EHR, medical claims, and EMA data).

2.2 Study Design and Outcomes (full description in Section 14.0)

Individuals who are active in medication treatment for opioid use disorder (MOUD) with buprenorphine for at least 2 weeks will be invited to participate in the study. This project will evaluate the feasibility and benefits of digital health technologies that can be embedded in clinical trials. Feasibility will be evaluated by the percentage of eligible participants who enroll and adhere to a 12 week period of assessment using passive mobile sensing devices (smartwatch and smartphone), daily randomly prompted EMAs (that assess sleep, stress, pain severity, pain interference, pain catastrophizing, craving, withdrawal, substance use risk context, mood, context, substance use, self-regulation, MOUD adherence, and impact of COVID-19), self-initiated substance use EMA, and social media data download. Participating in the social media data download portion of the study will be optional. The secondary outcomes will be treatment retention and buprenorphine adherence through EMA and EHR/medical claims data over 12 weeks (specifically, the 12 weeks of study participation as well as the 12 months prior to when the individuals start EMAs).

2.3 Sample Size and Study Population

Participants in the study will include approximately 50 (if recruitment is faster than anticipated, we will recruit up to 75) individuals who at the time of consent are active in MOUD with buprenorphine for at least 2 weeks prior to study enrollment. The study population will include males and females, age 18 and older, English-speakers, identified from Kaiser Permanente in Northern California (KPNC) members who have received treatment at one of KPNC's Addiction Medicine Recovery Services programs.

2.4 Treatment/Assessment/Intervention and Duration

This is an observational study designed to (1) evaluate the feasibility and utility of digital health technology in a MOUD treatment population, and (2) capitalize on the availability of EHR data to relate passive and active sensing data to treatment retention and medication adherence. This feasibility study will be conducted rapidly (e.g., within 1 year plus time to data lock) to generate data that can inform other HEAL (Helping to End Addiction Long-term℠) Initiative studies and clinical trials of populations with OUD.

Eligible participants are identified through EHR records, sent an invitational letter through secure message, and then called to recruit and screen. Following verbal consent to screen, research staff will perform a screening assessment over the phone/video to determine preliminary study eligibility prior to scheduling the baseline phone/video visits. Following electronic signed informed consent, the Baseline assessment will consist of interviewer-administered measures examining participant characteristics, current substance use (e.g., tobacco, alcohol, opioids, and other drugs), and substance use and mental health disorders. In addition to the screening and baseline assessments, the participants will be asked to wear a smartwatch and carry a smartphone continuously for a period of 12 weeks. The smartwatch will passively collect data regarding distance traveled, physical activity (including metrics of energy expenditure and steps), sleep, and heart rate. Also, participants will be prompted to respond to questions through a smartphone (i.e., EMA) up to 3 times daily for 12 weeks. Responses to these questions (which include questions regarding sleep, stress, pain severity, pain interference, pain catastrophizing, craving, withdrawal, substance use risk context, mood, context, substance use, self-regulation, MOUD adherence, and impact of COVID-19) will take approximately 10 minutes to complete at each prompting. In addition to the EMA prompts, individuals will be asked to self-initiate EMAs if substance use occurred. The responses to the self-initiated EMAs will take roughly 5 minutes to complete. App usage, audio/conversation, call/text, GPS, screen on/off, phone lock/unlock, phone notification

information, Wi-Fi & Bluetooth logs, sleep, ambient light, and proximity will be passively collected via smartphone. After the 12-week active study phase, participants complete a follow-up phone/video visit. At the follow-up phone/video visit, research staff will administer an interview-based assessment to measure current substance use (e.g., tobacco, alcohol, opioids, and other drugs), participant experience with the study devices (including wearing the smartwatch, carrying the smartphone, and responding to EMAs), treatment utilization, reasons for drop out (if appropriate), medication use/dose (if applicable), and overdose. For those who consent, social media data will be downloaded by the participant directly from the social media platform to a secure server using a remote desktop at the beginning of the study and at the end of the study. EHR and medical claims data (e.g., pharmacy claims data for Kaiser and non-Kaiser pharmacies if a claim was paid for) will be extracted 16 weeks after study completion (data will be collected 12 months prior to EMA start through 12 weeks after EMA start). Prior to each encounter (screening, baseline and follow-up), research staff will administer a brief prisoner status assessment to confirm study eligibility (non-prisoner status).

2.5 Safety Reporting

As this is an observational, non-intervention study, study-related Safety Events are anticipated to be rare. Nevertheless, this population is at elevated risk for overdose and other medical and psychiatric problems, and safety events may be elicited at baseline or spontaneously reported to study staff at any time while individuals are participating in the study. All project/site staff will be trained to recognize and report any safety event as described in Section 15.16. Safety events involving human participants, include, for example, suicidal ideation.

The study has a Study Clinician who will review each safety event as it occurs, and details of the safety event will be recorded in a secure database. Safety events requiring reporting to the Kaiser Permanente Northern California Institutional Review Board will be reported. All events that are serious, related and unexpected, or that place subjects at greater risk of harm will be promptly reported to Kaiser IRB (IRB of Record), as outlined in KPNC IRB guidance (policy # N-CRSP HRP 071). The Lead Investigators will be responsible for reporting to external parties (including Kaiser IRB).

The NIDA Program Officer must be informed of any death occurring during the study or coming to the attention of the study staff during the protocol-defined follow-up period. This report is made to NIDA regardless of whether the death was study related or unanticipated.

2.6 Analyses (Full Description in Section 14.0)

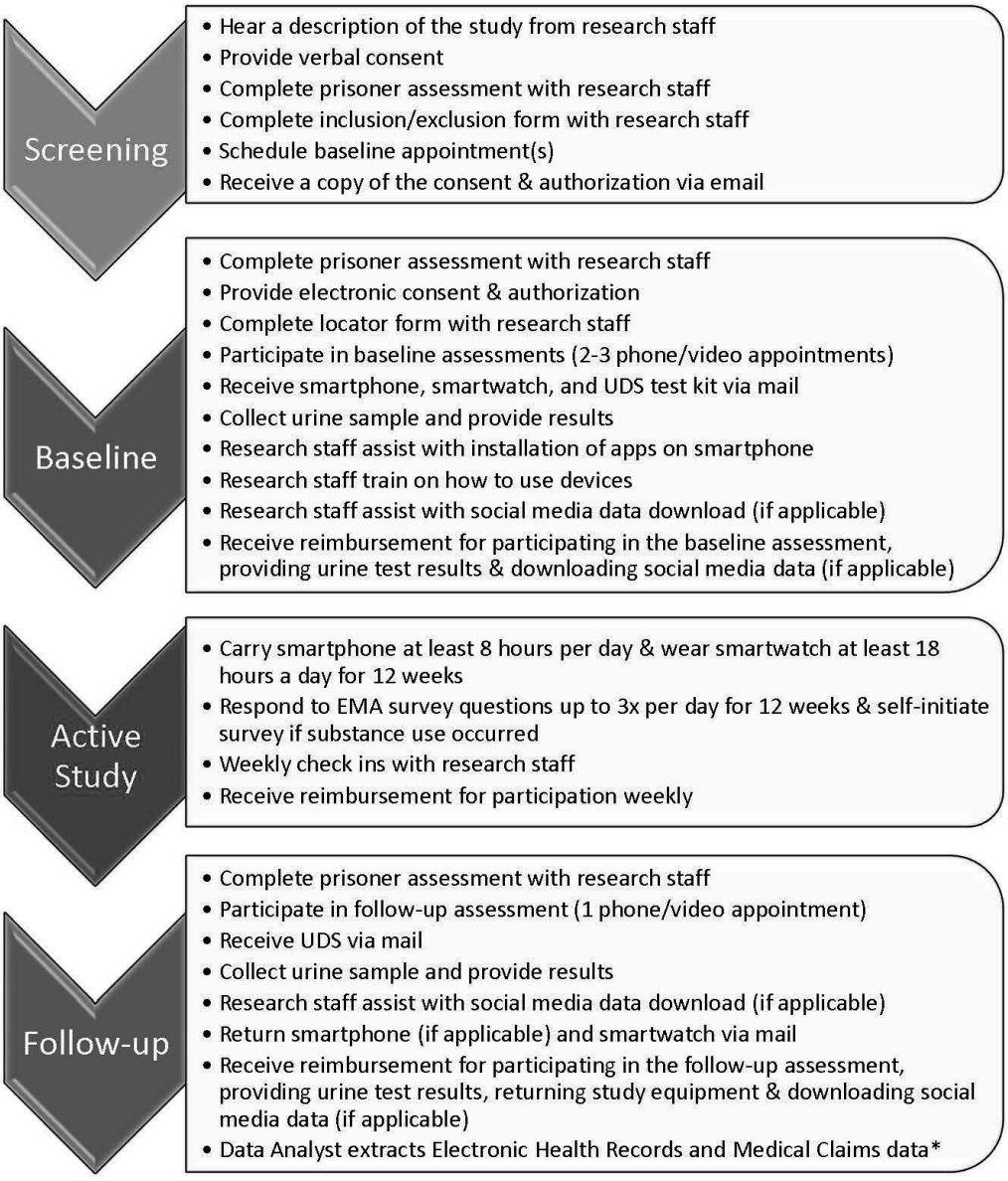
In order to measure the feasibility of digital health technology, we will generate descriptive statistical summaries of the level of adherence of study participants to the desired protocol (e.g., EMA response rate, smartwatch and smartphone wear/carry rate). No statistical inference is planned for this assessment. Feasibility will be evaluated via the following three independent metrics: 1) the percentage of days during the 12-week active phase enrolled participants wore/carried the smartwatch and smartphone; 2) the response rate to EMA prompts during the 12-week active phase; and 3) the percentage of participants who consent to social media data download and sparsity of social media data per participant.

In digital health data (Jain, Powers, Hawkins, & Brownstein, 2015a), the spatio-temporal granularity of information about an individual is of higher resolution than that obtained through cross-sectional or traditional longitudinal studies. Therefore, we define endpoints (dependent variables) that may occur repeatedly over a 12-week observational period, and aim to use data from smartphones, wearable devices, social media and EMA to predict, explain and detect these endpoints.

Our analyses comprise three main efforts: Predicting endpoints using passively and actively collected digital health and social media data; Explaining temporal-causal relationships between factors determined to be useful for predicting endpoints; Detecting event-specific endpoints using passively collected digital health and social media data.

Our approach to prediction will include regression-based methods (e.g., logistic regression), but we will also use common machine learning approaches for binary classification (e.g., random forest, support vector machines, K-nearest neighbor, gradient boosting). Although machine learning methods may often be more effective for prediction than regression-based methods, they may be difficult to explain, or may not reveal insights regarding the relationships between factors. Therefore, we also include a set of analyses that are conducive to generating such explanatory or descriptive insights. For example, we will apply supervised metric learning and prototypical case-based reasoning (Hsueh, Das, Maduri, & Kelly, 2018), topic-modeling (e.g., Latent Dirichlet Allocation) and causal inference methods (Hernan & Robins, 2006; Donald B. Rubin, 1974) (Kleinberg & Hripcsak, 2011). For detecting endpoints that currently rely on actively collected ecological momentary assessment, we will attempt to use only passively collected data to correctly classify whether the endpoint of interest has occurred.

3.0 STUDY SCHEMA



*Note: EHR/Medical Claims data will be extracted by the Data Analyst approximately 16-weeks after completion of study and includes data 12 months prior to EMA start through 12 weeks post-EMA start.

3.1 Key Research Site Roles

Site Principal Investigator (Site PI): The Site PI is the PI for the study who is at the site where research is taking place. This person is responsible for the oversight of study staff at the site and all aspects of protocol implementation at the site(s).

*If the Site PI is not a PhD or PsyD (Clinician), then an additional role of Study Clinician (PhD or PsyD) is required to review Safety Events.

Site Project Manager (Site PM): The Site PM is responsible for the oversight of RC/RAs at the site(s) and all aspects of study implementation at the site(s).

Research Coordinator (RC) and/or Research Assistant (RA). The RC/RA is responsible for working with the Site PI to ensure all aspects of the study are being implemented and followed according to the protocol at the site. The RC/RA will focus on; recruitment, participant communication, administering assessments, data collection/cleaning, study supply tracking, and working with local Node staff and the Lead Node to review and monitor study progress.

4.0 INTRODUCTION

4.1 Background and Significance to the Field

4.1.1 Study Rationale

Across the U.S., the prevalence of OUD and the rates of opioid overdoses have risen precipitously in recent years. Drug overdose is being called a “modern plague” (Katz, 2017) and is now the leading cause of death of Americans under age 50, having surpassed peak death rates from gun violence, HIV, and car crashes (Centers for Disease Control and Prevention (CDC), 2018; Katz, 2017). This dramatic spike in OUD has also been accompanied by marked increases in injection-related infections (including infective endocarditis and Hepatitis C) (Centers for Disease Control and Prevention (CDC), 2016, 2017; Hartman et al., 2016; Keeshin & Feinberg, 2016), babies born with Neonatal Opioid Withdrawal Syndrome (Patrick, Davis, Lehmann, & Cooper, 2015) and healthcare and criminal justice costs (Rhyan, 2017).

Although many factors have been shown to predict non-adherence in substance use disorder treatment (Simon et al., 2017; Weinstein et al., 2017); very few have been shown to be consistent across samples and most explain limited amounts of variance in outcome (DeVito, Carroll, & Sofuoglu, 2016). Most studies have examined a small set of potential moderators or mediators of outcomes in treatment retention and medication adherence for OUD, and thus may have led to over-simplified conceptions of a highly heterogeneous disorder.

Advances in **digital technologies and data analytics** have created new opportunities to assess and modify health behavior and thus accelerate the ability of science to understand and contribute to improved health behavior and health outcomes. Given the ubiquity of access to digital technology worldwide, digital technologies afford new opportunities to examine within-person differences in health behavior through intensive collection of individual-level data using mobile devices, wearable sensors, continuous monitoring, and mapping digital footprints. Digital technologies can also enable widespread reach and scalability of evidence-based, anytime/anywhere access to personalized interventions (Marsch, Lord, & Dallery, 2014). Specifically, mobile technologies enable EMA, (Shiffman, Stone, & Hufford, 2008) a method that prompts individuals to respond to queries (e.g., regarding positive and negative affect, context, access to opioids, urge to use (craving), drug use, withdrawal, perceived stress, sleep/sleep disturbance, and perceived pain) on mobile devices, and which enables “automated hovering” (Asch, Muller, & Volpp, 2012) or real-time monitoring, of individuals’ behavior while they engage in everyday activities and over time. The frequent, longitudinal assessment afforded by EMA in naturalistic contexts may clarify the dynamic role of mechanisms, or reveal new mechanisms, contributing to health behavior (McCarthy et al., 2008) in individuals who use opioids or who are in treatment for opioid use.

Digital technologies also enable **passive sensing and inference** from smartphones or sensing devices worn on the body, which is transforming how we understand human behavior, including health behavior. These mobile sensing technologies enable the continuous measurement of physiological and behavioral data in the real world as individuals move through their daily lives. This sensor data can be wirelessly streamed to a smartphone and processed in real-time on the mobile device to infer information about an individual’s behavior, health, and environment. These data from sensors can be combined with data from self-report EMA assessments embedded on mobile devices for real-time inference of environmental, social, and behavioral conditions (Marsch, 2018a, 2018b). In the future, this information could be used to prompt the delivery of interventions in real time (e.g., interventions that are directly responsive to the behavioral health

needs of an individual, such as a depressive state or craving of a substance of abuse) (Burns et al., 2011; Gustafson et al., 2014).

Further, the use of **social media** sites (e.g., online forums, social blogs) has exploded in recent years. Social media enables multi-directional communication anywhere and anytime. Social media data have been used to predict many phenomena, ranging from purchasing patterns to health epidemics (Brownstein, Freifeld, & Madoff, 2009; Darden & Perreault, 1976). A growing body of literature is showing how social media data may enable a rich understanding of the topology and functioning of social networks and their relationships to health/risk behavior (Kazemi, Borsari, Levine, & Dooley, 2017; S. J. Kim, Marsch, Brunette, & Dallery, 2017; S.J. Kim, Marsch, Hancock, & Das, (Forthcoming 2017); Naslund, Kim, et al., 2017). For example, social media has been shown to contain signals of depression among individuals, such as via predictors of decreased social activity, increased negative affect, highly clustered egocentric networks, and heightened concerns about relations and medications (Choudhury, Gamon, Counts, & Horvitz, 2013). Data derived from Facebook has been shown to predict a range of attributes including use of addictive substances (Kosinski, Stillwell, & Graepel, 2013); however, these have not been explored in individuals with OUD.

Digitally-derived, empirical data can markedly refine and advance our understanding of **health behavior**. These data allow for the development of dynamic models of health behavior to understand behavior in real-time and in response to changing environmental, social, physiological, and intrapersonal factors (Naslund, Aschbrenner, et al., 2017; Spruijt-Metz & Nilsen, 2014). Digital health technology methodologies have enabled new insights into several areas of health behavior, including mental health disorders and physical well-being. (Barnett et al., 2018; Onnela & Rauch, 2016). Results from this study may help identify useful digital data sources that may enhance outcomes measurement in clinical trials by allowing for the assessment of dynamic interactions between treatment and symptom response (Mofsen et al., 2019; Nugent, Pendse, Schatten, & Armey, 2019; Roos & Witkiewitz, 2017).

4.2 Innovation

- The project would be the first in this population to employ passive mobile sensing; social media data; and active responses to queries on mobile devices using ecological momentary assessment (EMA) that assess sleep, stress, pain severity, pain interference, pain catastrophizing, craving, withdrawal, substance use risk context, mood, context, substance use, self-regulation, MOUD adherence and impact of COVID-19 to obtain moment-by-moment quantification of an array of individual-level data that may predict treatment retention and medication adherence (in response to changing environmental, social, physiological, and intrapersonal factors).
- Use of novel analytic methods, including machine learning, is also innovative.
- Use of EHR to track MOUD retention and adherence is innovative, leverages existing CTN infrastructure to reduce patient burden, and, by definition, focuses on a “real world” outcome, thereby enhancing the potential clinical utility.

5.0 OBJECTIVES

5.1 Primary Objective

The primary objective of this study is to evaluate the feasibility of 1) utilizing digital health technology (EMA and digital sensing) to collect data continuously over a 12-week period and 2) collecting social media data.

5.2 Secondary Objective(s)

The secondary objective is to examine the utility of EMA, digital sensing, and social media data (separately and compared to one another) in predicting OUD treatment retention, and buprenorphine medication adherence (as captured in EHR, medical claims, and EMA data).

6.0 STUDY DESIGN

6.1 Overview of Study Design

Individuals with OUD who are active in outpatient buprenorphine treatment for at least 2 weeks will be recruited for the study. Potentially eligible individuals will be identified through the EHR and sent an invitational letter through secure message. Subsequently, study staff will call potential participants, and individuals interested in the study will go through a verbal consent process and complete the screening assessment by phone/video. Once it is confirmed that eligibility criteria are met, the participant will provide electronic informed consent and complete the baseline assessment by phone/video. The baseline appointments will take approximately 2.0 hours to complete, which will be done in two to three visits (preferably in two visits). Participants will wear a smartwatch and carry a smartphone (a study-supplied one or their own) that will passively collect sensor data. They will be asked to actively respond to EMA prompts through a smartphone up to 3 times daily and to self-initiate EMAs daily if substance use occurred over the 12 week study. For those who consent, social media data will be downloaded by the participant directly from the social media platform to a secure server using a remote desktop at the beginning of the study and again at the end of the study. EHR and medical claims data extraction will occur at approximately 16 weeks after study completion and will collect data 12 months prior to EMA start through 12-weeks post-EMA start. A follow-up assessment (taking approximately 45 minutes to complete assessments plus 15 minutes to instruct participants on how to return study equipment) will occur approximately 12 weeks post-EMA start by phone/video.

6.2 Duration of Study and Visit Schedule

Participants will complete screening by phone/video (approximately 10 minutes) and two to three baseline phone/video appointments which will take approximately 2.0 hours. The study involves a 12-week active phase wherein participants will wear a smartwatch, carry a smartphone, and respond to EMA prompts and self-initiated EMAs through a smartphone. For those who consent, social media data will be downloaded by the participant directly from the social media platform to a secure server using a remote desktop at the beginning of the study and again at the end of the study. A follow-up phone/video appointment (approximately 60 minutes) will occur approximately 12 weeks post-EMA start. EHR and medical claims data will be extracted by the research staff approximately 16-weeks after study completion and includes data 12 months prior to EMA start through 12 weeks post-EMA start.

7.0 OUTCOME MEASURES

7.1 Primary Outcome Measure

Primary outcome measures will include:

1. Feasibility - the percentage of days during the 12-week active phase enrolled participants wore/carried the smartwatch and smartphone;
2. Feasibility - response rate to EMA prompts during the 12-week active phase; and
3. Feasibility - the percentage of participants who consent to social media data download and sparsity of social media data per participant.

7.2 Secondary Outcome Measure(s)

The secondary outcome measures will include:

1. OUD treatment retention (days retained in OUD treatment program) based on EHR data;
2. Days covered on MOUD based on EHR and EMA data; and
3. Non-prescribed opioid use (including illicit opioid use) based on EMA data.

7.3 Other Outcome Measures

Other outcomes will include:

1. Frequency of missed buprenorphine doses based on EMA data;
2. Percentage of days with access to prescription medication exceeding a threshold (e.g., 80%) over the 12-week study period (a dichotomous variable based on pharmacy dispensation and medication orders from the EHR data extraction);
3. Number of days of non-prescribed opioid use (including illicit opioid use) in the last 4 weeks (weeks 9-12 post study consent) based on EMA data; and
4. Each non-prescribed opioid use event during the 12-week study period based on EMA data.
5. Each missed dose event during the 12-week study period based on EMA data.
6. Each missed visit to OUD treatment program during the 12-week study period based on EHR data.

7.4 Study Timeline

After receiving NIDA Center for Clinical Trials Network (CCTN) approval of the full/final protocol, approximately 6 months of trial preparation activities will elapse prior to commencing enrollment. Study preparation will include obtaining IRB approval, developing the data collection systems, refining the manual of procedures (MOP), hiring and training staff, and endorsing sites. We anticipate the study may be implemented in a single wave; however, sites may launch on a rolling basis if necessary.

The research team will develop and refine the digital health data collection software, as well as, the data tracking and storage database (a duration of approximately 4 months). We will examine all procedures with approximately 5 individuals, during their first several weeks of study involvement, to ensure any potential glitches with the EMA prompt scheduling, sensor data collection, and/or data transfer are identified and if necessary, make further adjustments. Recruitment for the digital component is expected to take approximately 6 months. Follow-up assessments and social media (if applicable) data download will be completed approximately 3

months after the last participant is enrolled. EHR and medical claims data extraction will be completed approximately 4 months after the active phases of study ends. Therefore, data lock is projected to be completed approximately 20 months after CCTN approval of the final protocol.

Months 1-6: Study preparation

Months 7-12: Recruitment

Months 9-15: Active phase ends for participants

Months 16-20: Data Lock (staggered lock depending on data source: sensor/EMA, social media, EHR/medical claims)

8.0 STUDY POPULATION

Approximately 50 (if recruitment is faster than anticipated, we will recruit up to 75) individuals who are active in outpatient buprenorphine treatment for at least two weeks. Participants will include males and females, aged 18 years or older, across all racial and ethnic categories. We will recruit from the Addiction Medicine Recovery Services (AMRS) program at Kaiser Permanente in Northern California (KPNC), which is part of the Health Systems Node. The KPNC AMRS programs provide integrated SUD treatment, including buprenorphine and other services.

8.1 Participant Inclusion Criteria

Individuals participating in the study must:

1. Have been active in Kaiser outpatient buprenorphine treatment for OUD for the past 2 weeks (determined at screening);
2. Be ≥18 years old (determined at screening);
3. Be able to understand English (determined at screening);
4. Be available to participate in the full duration of the study (12 weeks) (determined at screening);
5. Have an active email account and willing to provide the email address to researchers (determined at screening);
6. Permit researchers to access personal electronic health record (EHR) and medical claims data (determined at screening);
7. Be willing to carry and use personal or study provided smartphone for 12 weeks (determined at screening); and
8. Be willing to wear a smartwatch continuously (except during pre-defined activities such as showering) for 12 weeks (determined at screening).

8.2 Participant Exclusion Criteria

Participants will be excluded from the study if they:

1. Are unwilling or unable to provide informed consent (determined during the Consent process and during Consent Quiz); and
2. Are currently in jail, prison or other overnight facility as required by court of law or have pending legal action that could prevent participation in study activities (determined by Prisoner Status Assessment at each study visit).

8.3 Strategies for Recruitment and Retention

Potentially eligible patients will be identified in the electronic health record and sent an invitational recruitment letter/secure message. Within approximately a week of mailing recruitment letters/sending a secure message, research staff will contact participants by phone to determine if they are interested and eligible, using the IRB-approved recruitment script, verbal consent and screening questions.

Study participants will be compensated $75 for completing the Baseline appointments and baseline urine drug screen, and $100 for completing the 12-week Follow-up appointment and follow up urine drug screen.

During the 12-week active phase of the study (the 12 weeks of EMA and sensor data collection via smartphone and smartwatch), research staff will contact participants to encourage them to continue their participation and/or troubleshoot any problems that may arise with their smartphone, smartwatch or EMA. Staff will also contact (e.g., call, text, email) participants if sensor data is not being recorded from the smartphone, smartwatch and/or if there is a lapse in responding to EMA prompts on the smartphone. If there are unexpected issues or problems with the technology (study equipment, study apps, social media download) that research staff cannot resolve with the participant, research staff may need to contact technical support personnel at Dartmouth using a 3-way or conference call to assist the participant with troubleshooting technical issues.

To be considered engaged in the study, an individual must respond to a minimum number of EMA prompts and have recorded a minimum number of smartphone/smartwatch sensor data on 7 out of the first 14 days of study participation. An individual will be contacted via phone, text, and/or e-mail by research staff after two days with no EMA or sensor data collected. If an individual does not meet the engagement criterion AND is non-responsive to research staff outreach in the first 14 days of study participation, then the individual will be considered a “non-engager” and the study team will continue to recruit until 50 (if recruitment is faster than anticipated, we will recruit up to 75) “engaged” individuals are enrolled. Non-engagers will not be withdrawn from the study, as we will attempt to collect all possible data from all participants.

To aid retention and adherence with the digital health data collection, participants will be compensated up to $21 per week for completing EMAs, up to an additional $10 per week bonus for completing a minimum of 80% of received EMAs, and up to $14 per week for carrying their smartphone at least 8 hours per day and wearing the smartwatch at least 18 hours per day. At the end of the 12-week active phase of the study, participants will receive a $50 bonus for either using their personal smartphone (to help offset the cost of their data plan) or returning a study-provided smartphone, and a $50 bonus for returning the study-provided smartwatch. Finally, participants who consent to the social media portion of the project will receive up to an additional $180. Total possible compensation will be up to $820 over the course of the 12-week active study phase. In addition to the earnings and bonuses (described above), an individual who completes a minimum of 80% of received EMAs within a given week will qualify for a drawing at the end of that week where the individual could win a $50 prize. Each individual will have an opportunity to participate in up to 12 drawings over the 12 weeks. During the 12-week active study phase, any incentives, bonuses, and/or drawings earned will be uploaded weekly to a reloadable debit card.

Total compensation will be up to $995 for participating in all study activities.

9.0 SITE SELECTION

9.1 Number of Sites

We will recruit approximately 50 (if recruitment is faster than anticipated, we will recruit up to 75) participants from KPNC (part of the Health Systems Node) who have had treatment at KPNC's Addiction Medicine Recovery Services (AMRS) programs.

9.2 Site Characteristics

The AMRS programs at Kaiser Permanente Northern California (KPNC) offer a broad range of services (medical services onsite, group and individual therapy, family therapy). Staffing includes physicians, social workers, and substance use counselors. The AMRS programs offer MOUD treatment for buprenorphine.

We anticipate roughly 180 patients with OUD on buprenorphine for at least 2 weeks will be approached for recruitment. Assuming a conservative 30% recruitment rate, we anticipate approximately 50 (if recruitment is faster than anticipated, we will recruit up to 75) patients enrolled over the 6-month study recruitment period.

9.3 Rationale for Site Selection

KPNC was selected based on its ability to (1) provide access to individuals who are in MOUD buprenorphine treatment and (2) provide access to EHR data on treatment retention, medication adherence, and service utilization. KPNC serves a mixed population (in terms of severity) of individuals in treatment for OUD. KPNC is an integrated healthcare system that maintains a data repository, the Virtual Data Warehouse, which has combined EHR data (e.g., demographics, membership, diagnoses, service utilization, pharmacy, lab data) with several other data sources, including medical claims data (e.g., non-Kaiser pharmacy data). Participant EHR data will include urine toxicology results, buprenorphine dispensation data, and treatment utilization data (e.g., substance use, primary care, psychiatry, emergency department, inpatient, phone appointments, secure messages) which reflects any encounters with the health system.

10.0 STUDY PROCEDURES

10.1 Screening

Patients will be screened by phone/video to determine eligibility. After briefly explaining the study, conducting prisoner assessment and obtaining verbal consent, research staff will perform the screening and complete the Inclusion/Exclusion form. If eligible, research staff will schedule the initial baseline phone/video appointment and send consent documents to participant for their review before their appointment. (see Section 11).

The screening will take approximately 10 minutes to complete.

10.2 Consent and Baseline

10.2.1 Informed Consent Procedures for Participants

Informed consent will be obtained by phone/video and documented online using an electronic signature. Participants will have been given an opportunity to review consent documents prior to the baseline phone/video appointment (see 10.1). At the initial baseline phone/video appointment, research staff will review all elements of consent with participant over the phone/video (procedures, risks, benefits, compensation, etc.) and provide an opportunity for participant to ask questions.

Once questions are answered, the participant will be asked to pass a brief consent quiz to document comprehension of the study activities. Any incorrect responses will be reviewed with the participant by research staff. After providing an electronic signature, participants will be able to print a copy of the forms to keep for their records. The informed consent process and quiz will take approximately 30 minutes to complete. Patients will be provided two opportunities to pass the quiz, at which point they will be determined ineligible.

10.2.2 HIPAA Authorization and Medical Record Release Forms

The study site will obtain authorization from participants for use of protected health information, such as access to their EHR and medical claims data. The site will be responsible for communicating with their IRB(s) or Privacy Boards and obtaining the appropriate approvals or waivers to be in regulatory compliance.

10.2.3 Baseline

The baseline will be conducted in two or three phone/video appointments: the first appointment will consist of informed consent and the baseline assessment, and the second appointment will consist of urine drug screen, setting up study devices, installing study applications (“apps”), and learning to use devices and apps. If needed, appointments will be conducted with HIPAA compliant IRB-approved video capability.

Initial baseline appointment (1 hour): After conducting prisoner assessment and providing informed consent, participants will complete the Baseline assessment (see Section 11). The Baseline assessment consists of interviewer-administered measures examining participant characteristics, current substance use (e.g., tobacco, alcohol, opioids, and other drugs), substance use and mental health disorders, and the impact of COVID-19.

Once the first Baseline appointment is completed, participants will be mailed their urine drug screen (UDS) kit, their smartwatch and study smartphone (if applicable) and technology training documentation.

Second Baseline appointment (1 hour): Once the equipment is received, research staff will schedule a second phone/video appointment with participant to review the urine collection and technology training documentation. Research staff will walk through the set-up, use and care of smartphone and smartwatch, installation of the study app and the Garmin Connect app, as well as instructions for initiating and completing the daily EMAs. Research staff will also instruct participants to collect urine sample and upload results. If any technical issues arise, the research staff have the ability to upload the photographs into REDCap for the participant. Once the urine drug screen results are received, participants will be reimbursed $75 (via gift card) for completion of the baseline.

A third baseline appointment can be arranged if needed. We don't anticipate this will occur frequently as the tasks should easily be completed within two baseline appointments.

Research staff will explain to participants that EMA data will not be monitored in real-time, and participants will be instructed to call their medical providers or 911 if they have an immediate crisis or an emergency.

Participants will be instructed on how to download social media (for those who consented to this part of the study). Social media data will be downloaded by the participant directly from the social media platform to a secure server at Dartmouth using a remote desktop at the beginning of the study.

Additional compensation will be provided for social media data download, as well as participation in the active phase of the study (completing EMAs, wearing the smartwatch and carrying the smartphone) (described in Section 8.3).

If there are unexpected issues or problems with the technology (study equipment, study apps, social media download) during the active phase of the study that research staff cannot resolve with the participant, research staff may need to contact technical support personnel at Dartmouth using a 3-way or conference call to assist the participant with troubleshooting technical issues.

10.3 Premature Withdrawal of Participants

All participants will be followed for the duration of the study unless they withdraw consent, die, or the investigator or sponsor decides to discontinue their enrollment for any reason. Reasons for the investigator or sponsor terminating a participant from the study may include, but are not limited to, the participant becoming a threat to self or others.

Participants may withdraw voluntarily from the study at any time.

10.4 Study Halting Rules

As this is not a clinical trial and no treatment involved, risk is expected to be very low. There will be no study halting rules.

10.5 Follow-Up

A follow-up assessment will be completed approximately 12 weeks post-EMA start by phone/video. Research staff will administer an interviewer-based assessment to measure current substance use, participant experience with the study devices, treatment utilization, reasons for drop out (if appropriate), employment, insurance coverage, medication use/dose (if applicable),

and overdose. Participants will be mailed a UDS kit and asked to collect sample and upload test results to REDCap. If any technical issues arise, the research staff have the ability to upload the photographs into REDCap for the participant. Once the UDS results are received, participants will receive $100 for completing the follow up assessment. Additionally, EHR, medical claims, and social media (if consented) data will be extracted/downloaded after participants complete the 12-week active phase of the study. Additional compensation will be provided for social media data downloads (if consented) and returning study equipment at the end of the active study phase (described in Section 8.3).

10.6 Participant Reimbursement

Participants will be compensated for their participation in this study (incentives described in Section 8.3). Compensation will be in accordance with the IRB of record's policies and procedures, and subject to IRB approval. Total compensation will be up to $995 for participating in all study activities ($75 for baseline assessment, $100 for follow up assessment and up to $820 for engagement in digital data collection). Payments for research participation in excess of $600.00 in one calendar year are reportable to the Internal Revenue Service (IRS). Participants may be required to pay taxes on this money, as required by law, and will be asked to provide home address and social security number to receive study payments in excess of $600.

11.0 STUDY ASSESSMENTS

11.1 Table of Study Assessments

Construct	Subdomain	Assessment Name	Interview (I) Extraction (E) Download (D)	Time estimate (minutes)
	Verbal Consent	Verbal consent	I	5
Screening	Prisoner Status	Prisoner Status Assessment (Repeat Prisoner Status Follow-up at each study visit	I	2
	Study eligibility	Inclusion/Exclusion Form	I	3
			Total Time	**~10 minutes**
Baseline	Prisoner Status	Prisoner Status Assessment	I	2
	Consent/Locator	E-Consent E-HIPAA Authorization Consent Quiz Locator Form (to be completed at each call)	I	30
	Demographics Substance Use	PhenX Core Tier 1, PhenX Core Tier 2, NSDUH (subset of measures/question: demographics & current substance use)	I	25
	COVID-19	Baseline Assessment	I	2
	DSM-5 diagnosis	NetSCID-5	I	20-45
	Recent use	Urine Drug Screen	I	10
			Total Time	**~85-120 minutes**

	Social Media	Social media images/texts of postings & comments, reactions, date/time	D- from social media platform via remote desktop	At the beginning of the study
	Prisoner Status	Prisoner Status Assessment	I	2
Follow-up	Substance Use	PhenX Core Tier 1 (subset of measures: current substance use)	I	20
	Participant Experience Employment Treatment utilization Insurance coverage	Follow-up Assessment		15
	Recent use	Urine Drug Screen	I	10
			Total Time	**~60 minutes***
	Social Media	Social media images/texts of postings & comments, reactions, date/time	D- from social media platform via remote desktop	At the end of the study
	Health records	EHR	E**	Retroactively from 12 weeks post-EMA start to 12-months prior to EMA start
	Health records	Medical Claims	E**	Retroactively from 12 weeks post-EMA start to 12-months prior to EMA start

*Follow-up appointment will take approximately 45 minutes to complete assessments plus another ~15 minutes to instruct participants on how to return study equipment (for a total of approximately 60 minutes).

**Note: EHR/Medical Claims data will be extracted by the Data Analyst approximately 16-weeks after completion of study and includes data 12 months prior to EMA start through 12 weeks post-EMA start.

11.2 Active Study Phase Digital Health Assessments

Construct/ domain	Subdomain	Assessment name	Wearable (W) Carryable (C) Self-report (SR)	Occurrence
Smartwatch/ Smartphone/ Self-Report	Distance, physical activity, sleep	Ambulatory Physiological Assessment using Mobile Sensors	W	Wear at least 18 hours/day, data transmitted real-time for 12 weeks
	Phone activity, WiFi/Bluetooth logs, ambient light, proximity, location, audio/conversation	Passive Assessment using Mobile Sensors	C	Carry smartphone at least 8 hours/day, data transmitted real-time, for 12 weeks
	Ecological Factors	Ecological Momentary Assessment (EMA) (including self-report of drug use)	SR	Up to 3x/day for 12 weeks
	Self-Regulation	Momentary Self-Regulation Scale 12-item	SR	Up to 3x/day for 12 weeks

11.3 Description of Measures

11.3.1 Prisoner Status Assessment

Prisoner status must be assessed for each participant at each separate encounter (i.e., all study contacts [e.g., screening appointment, baseline appointments, and follow-up appointment], as this study will not apply for OHRP Prisoner Certification). Due to the high-risk nature of this population becoming involved in the criminal justice system, assessment is required.

11.3.2 Inclusion/Exclusion

This form will be used to obtain information on inclusion and exclusion criteria to document eligibility. Eligibility is assessed continually as appropriate. Only participants who continue to meet study eligibility criteria will be permitted to continue with study procedures.

11.3.3 Locator Form

A locator form is used to obtain information to assist in finding participants through the 12-week active and follow-up phase of the study. This form collects the participant's current address, email address, and phone numbers. In order to facilitate locating participants if direct contact efforts are unsuccessful, addresses and phone numbers of family/friends who may know how to reach the

participant are collected. This information will be collected at baseline and will be updated at each contact.

No information from this form is used in data analyses, nor is this information captured in the data capture system. The locator form is stored in a secure electronic folder with other participant PHI data.

11.3.4 PhenX Substance Abuse and Addiction Core Tier 1 (PhenX Core Tier 1)

The PhenX Core Tier 1 is a part of the Substance Abuse and Addiction Collections (https://www.phenxtoolkit.org/sub-collections/view/8) that are being adopted across NIDA-funded research. We are using the following subset of measures from the Core Tier 1: demographics (age, ethnicity, gender, race, current educational attainment, current employment status, and current marital status) and current substance use (tobacco, alcohol, and drugs) (Hamilton et al, 2011). The demographics (except for employment status) will only be collected at baseline, while current substance use and current employment status will be collected at baseline and follow-up.

11.3.5 PhenX Substance Abuse and Addiction Core Tier 2 (PhenX Core Tier 2)/National Survey on Drug Use and Health (NSDUH)

The PhenX Core Tier 2 (https://www.phenxtoolkit.org/sub-collections/view/9) is a complementary set of 8 measures to the PhenX Core Tier 1 (e.g., annual family income, child-reported parental education attainment, family history of substance use problems, household roster-relationships, internalizing, externalizing, and substance use disorders screener, occupation/occupational history, peer/partner substance use and tolerance of substance use, and social networks). We will only use a subset of questions from the Annual Family Income measure to get an estimate of total income of all family members (Hamilton et al, 2011). If the participant is unsure of the total family income, then we will use a subset of questions from the Substance Abuse and Mental Health Services Administration (SAMHSA)'s NSDUH survey to determine which income category best characterizes total combined family income (Center for Behavioral Health Statistics and Quality, 2017). Income will be collected at baseline only.

11.3.6 NetSCID-5

The Structured Clinical Interview for DSM-5 (SCID-5) is a semi-structured interview designed to assess substance use and mental health diagnoses (First et al, 2015). This study will use an electronic version of the SCID-5, the NetSCID-5, developed by TeleSage™. The TeleSage™ NetSCID-5 is fully licensed by the American Psychiatric Association and has been validated (Brodey, First, Linthicum, Haman, Sasiela, & Ayer, 2016). The NetSCID is HIPAA-compliant, and data is maintained on a secure, encrypted, and geo-redundant server. TeleSage™ has the capability of customizing the NetSCID-5 measure, so only modules relevant for this study will be selected (bipolar I disorder, major depressive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder, adult attention deficit hyperactivity disorder, alcohol use disorder, cannabis, stimulants/cocaine, opioids, PCP, other hallucinogens, inhalants, sedative-hypnotic-anxiolytic, and other/unknown).

At the end of the study, all data collected on the TeleSage™ platform and stored on their server(s) will be securely transferred to Dartmouth's server and expunged from TeleSage™'s server(s).

11.3.7 Urine Drug Screen

Urine drug screen kits (UDS), otherwise referred to as urine toxicology, will be mailed to participants, and participants will be asked to collect a urine sample, record and upload results to study team using a secure system (e.g. REDCap). In rare cases when there are technological issues with uploading the photos, the participant can send photos to research staff via text to a research staff member's Kaiser cell phone (which is KPIT approved). In this case, research staff will upload the photographs into REDCap for the participant. All urine specimens are collected using CLIA-Waived and FDA-approved one-step multi-drug screen test cup following the manufacturer's recommended procedures. The study will use the DrugConfirm™ Advance Urine Drug Test Kit which screens for: alcohol, amphetamine, barbiturate, buprenorphine, benzodiazepine, cocaine, fentanyl, MDMA [ecstasy/molly], methamphetamine, methadone, morphine 300 ng/mL, oxycodone, phencyclidine (PCP), tramadol and THC.

11.4 Follow-up

11.4.1 Follow-up Assessment

The follow-up assessment will collect the following: current substance use (e.g., tobacco, alcohol, opioids, and other drugs), current employment status, participant experience with the study devices (including wearing the smartwatch, carrying the smartphone, and responding to EMAs), treatment utilization, reasons for drop out (if appropriate), insurance coverage, medication use/dose (if applicable), and overdose.

11.5 Digital Health Technology

11.5.1 Ambulatory Physiological Assessment using Mobile Sensors

We will develop a smartphone application, that can sense and store contextual information about a participant, e.g., location, physical activity (steps), phone activity (non-identified audio information such as segments of silence, speech features such as pitch control and voice quality), app usage, call/text, screen on/off, phone lock/unlock, sleep, ambient light, and proximity (e.g., to user's ear). Features will be derived from the raw sensing streams to create multiple relevant contextual variables. This application will be installed directly on the study provided smartphone (Moto G7 Power) or on a participant's smartphone (if they have a compatible phone). The data collected will be stored on the smartphone and will be securely transmitted to a secure cloud-based database hosted at Dartmouth.

In addition to the smartphone, the participants will be provided with a smartwatch (Garmin Vivosmart 4). The participants will be asked to wear the smartwatch continuously (except during pre-determined exceptions periods, such as when the participants are showering or charging the device). In our experience, the Garmin Vivosmart 4 smartwatch (among others) is comfortable, lightweight, and has a long battery life and an easy-to-use interface. The device can reliably track distance traveled, physical activity (including metrics of energy expenditure and step count), sleep stages, as well as heart rate. Data from the Garmin smartwatch includes raw sensor data, like, heart-rate, and several high-level features computed by Garmin (using their proprietary algorithms including; sleep stage information, periods of light/deep sleep, stress levels, and others). This data will be transmitted to the Garmin Connect application installed on the smartphone, which would in turn send the data to Garmin cloud servers. Garmin will provide us with access keys for the research staff to pull the data from the Garmin servers to the cloud-based database at Dartmouth College.

11.5.2 Ecological Momentary Assessment (EMA)

Participants will be prompted up to 3 times per day over 12 weeks by the smartphone app to self-report sleep, stress, pain severity, pain interference, pain catastrophizing, craving, withdrawal, substance use risk context, mood, context, substance use, self-regulation, MOUD adherence, and the impact of COVID-19 (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989; Freeman & Gottfredson, 2018; Kuerbis et al., 2019; Preston et al., 2017, 2018). The EMA prompt delivery times will be randomized within each of the prompt timeframes (e.g., morning, mid-day, end of day). In addition to prompted EMAs, participants will be asked to self-initiate EMAs if substance use occurred (e.g., opioids, cocaine, or other stimulants). All EMA data collected via the smartphone will be securely transmitted to a secure cloud-based database housed in the Research Computing Department at Dartmouth College.

11.5.3 Momentary Self-Regulation Scale

This brief 12-item questionnaire assesses self-regulation on a momentary basis as individuals move through their lives (S. J. Kim et al., Under Review). This information will be collected up to 3 times daily over the 12-week study period by smartphone. All data collected via the smartphone will be securely transmitted to a secure cloud-based database housed in the Research Computing Department at Dartmouth College.

11.5.4 Social Media

Participants will be asked to download their social media data to a secure server using a remote desktop application. Images/texts of postings and comments as well as date/time and the number of reaction responses (e.g., Like, Sad, Angry) per posting and per comment will be extracted from the downloaded social media data through postprocessing for analysis. The download will occur at the beginning of the study and also at the end of the study. If participants have difficulty downloading the social media data, the research staff can provide guidance/instructions on how to download social media data and if needed can walk through the download process with the participant via phone or video. Should a technical issue arise that the research staff cannot resolve, research staff may need to contact technical support personnel at Dartmouth using a 3-way or conference call to assist with troubleshooting technical issues. All social media data will be securely stored on an encrypted server at the Williamson Translational Research Building in the Biomedical Data Science Department at Dartmouth College.

11.6 Other Measures

11.6.1 Electronic Health Records (EHR)

EHR data extraction will include all outpatient and inpatient encounters, medications (buprenorphine and others*), procedures, and diagnoses for the 12 months prior to EMA start and the 12-week study period. In addition, we will extract lab results from urine drug screens, patient demographic information, and insurance deductible level. We will extract appointment data to determine if visits were cancelled or missed. We will examine membership data to determine if the patient's membership became inactive in the study period. KPNC is an integrated healthcare delivery system, and the KPNC EHR includes both services provided inhouse and services obtained outside of KPNC, so long as the non-KPNC services were submitted as medical claims for reimbursement.

*Prescription data for opioids other than buprenorphine will be limited to patient-level dichotomous variables (yes/no) reflecting whether any non-buprenorphine opioid was ordered or dispensed during the time period.

11.7 Clinical and Safety Assessments

11.7.1 Safety Events

Safety events may be elicited at baseline or spontaneously reported to study staff at any visit following consent. Safety events suggesting medical or psychiatric deterioration will be brought to the attention of the Study Clinician for further evaluation and management. Safety events reporting are according to the reporting definitions and procedures outlined in the protocol and in accordance with applicable regulatory requirements. See Appendix A for details.

12.0 TRAINING REQUIREMENTS

12.1 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 Node and other participating Nodes, and subject matter experts, as applicable. The Northeast Node is the Lead Node.

The CTN-0084-A2 study staff will be trained as specified in the study Training Plan. Training will include Human Subjects Protection (HSP) and Good Clinical Practice (GCP) as well as protocol-specific training on assessments, study interventions, safety and safety event reporting, study procedures, data management, quality assurance, laboratory procedures, etc. The Lead Node and Local Node are responsible for development and delivery of study-specific training related to the study intervention(s) and procedures including data management, as well as, non-intervention training (e.g., regulatory and laboratory procedures, safety and safety event reporting, quality assurance and monitoring, etc.). 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), 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 Lead Node. As changes occur in the prescribed training, the Training Plan and training documentation tracking forms will be amended to reflect these adjustments.

13.0 CONCOMITANT THERAPY/INTERVENTION

13.1 General

Not applicable for this study.

13.2 Medications Prohibited/Allowed During Trial

There will be no medications prohibited during the trial. Based on what we know about the population at the study site, participants will be receiving buprenorphine medications for substance use; psychiatric medications; and, medications for physical/medical ailments, in addition to behavioral treatments.

14.0 STATISTICAL DESIGN AND ANALYSES

14.1 General Design

14.1.1 Study Hypothesis

Feasibility of digital health technologies: The collection of intensive longitudinal data requires participants to adhere to wearing and carrying a smartwatch and smartphone, respectively, consistently throughout the study. Participants are also expected to respond to assessment questions up to 3 times a day and self-initiate EMA if substance use occurred, on every day of the 12-week study. We hypothesize that the financial incentives provided to participants will adequately incentivize these adherence behaviors.

Understanding behaviors of patients in treatment: We hypothesize that, intensive longitudinal data capturing of patient context and psychological state (via EMA) will be useful for predicting treatment retention, and buprenorphine medication adherence.

14.1.2 Primary and Secondary Outcomes (Endpoints)

The primary outcomes will include: (1) the percentage of days during the 12-week active phase enrolled participants wore/carried the smartwatch and smartphone; (2) response rate to EMA prompts during the 12-week phase; and (3) the percentage of participants who consent to social media data download and sparsity of social media data per participant.

The secondary outcome measures will be: (1) OUD treatment retention (days retained in OUD treatment program) based on EHR data; (2) Days covered on MOUD based on EHR and EMA data; and (3) Non-prescribed opioid use based on EHR and EMA data.

14.1.3 Recruitment

Participants will be recruited from Kaiser Permanente Northern California patients who have been treated at the KPNC AMRS programs for OUD.

14.1.4 Randomization and Factors for Stratification

Does not apply to this study.

14.2 Rationale for Sample Size and Statistical Power

14.2.1 Projected Number of Sites

We plan to recruit from Kaiser Permanente in Northern California (KPNC).

14.2.2 Projected Number of Participants per Site

Approximately 50 (if recruitment is faster than anticipated, we will recruit up to 75) participants are projected to be recruited from KPNC.

14.3 Statistical Methods for Primary and Secondary Outcomes

For our primary and secondary outcomes, we intend to use measures such as precision, recall (sensitivity) and specificity, F-score, to assess the quality of our predictions. The quality of the

identified digital phenotypes will be evaluated using cohesion (e.g., Silhouette score) and endpoint-differentiating power (e.g., Z-score).

14.4 Significance Testing

The primary outcome will be evaluated using a two-sided test with a type I error rate of 5%. There are several secondary outcomes; however, multiple comparisons will not be adjusted for since these are not part of the study's primary objective as an observational study.

14.5 Types of Analyses

We are interested in measuring and predicting outcomes that may occur repeatedly over a 12-week observational period (e.g., patterns of daily drug use) using digital health technology. In digital health (Jain et al., 2015a) the spatio-temporal granularity of information about an individual is of higher resolution than that obtained through cross-sectional or traditional longitudinal studies. We will therefore assess the utility of using data from smartphones, smartwatches, social media and ecological momentary assessment to predict, explain and detect these outcomes.

Predicting outcomes using passively and actively collected digital health and social media data: Our approach to prediction will include regression-based methods (e.g., logistic regression), but we will also use common machine learning approaches for binary classification (e.g., random forest, support vector machines, K-means, gradient boosting). For each of these classification techniques, we will assess the utility of the various digital data for improving prediction quality. Typical evaluation methods used to assess the prediction quality include accuracy, precision, F-score, sensitivity (recall), and specificity. The relative utility of the various data for predicting outcomes will be assessed at two levels - individual features level and aggregated feature level. Interpretability of each feature and its contribution in predicting the outcome variable will be assessed using an ensemble framework, SHAP (Lundberg & Lee, 2017). In addition, we will also assess mutual information (Kraskov, Stogbauer, & Grassberger, 2004), which is a non-parametric approach of estimating the dependency between individual features and the target outcome. In another approach, features will be aggregated based on their gross categories (e.g., Facebook, Twitter, GPS, step, sleep, mood). The relative importance of each category will be evaluated based on its performance in predicting outcome (e.g., F-score).

1. *Explaining temporal-causal relationships between factors determined to be useful for predicting outcomes*: Although machine learning methods may often be more effective for prediction than simple regression or correlation, they may be difficult to explain, or may not reveal insights regarding the relationships between factors. Therefore, we also include a set of analyses that are conducive to generating such explanatory or descriptive insights. For example, we will apply supervised metric learning and prototypical case-based reasoning (Hsueh et al., 2018), topic-modeling (e.g., Latent Dirichlet Allocation) and causal inference methods (Cheng, Bahadori, & Liu, 2014; Kleinberg & Hripcsak, 2011).
2. *Outcome detection using passively collected digital health data*: We plan to measure drug use and medication non-adherence events via EMA, multiple times a day. Since EMA requires a level of active engagement from participants that may not be realistic to expect outside of a research study, we plan to use machine learning to detect these events using only passively collected data. The methods used here would be similar to the machine learning methods previously described for binary classification.
3. *Feasibility of digital health technology:* We will generate descriptive statistical summaries of the level of adherence of study participants to the desired protocol (e.g., EMA response rate, smartwatch and smartphone wear/carry rate). No statistical inference is planned for this assessment.

14.6 Interim Analysis

No planned interim analyses.

14.7 Exploratory Analysis

See Extended Data Analytic Plan for more details.

14.8 Missing Data and Dropouts

Missing data will be classified into three classes according to the characteristics of the randomness: missing not at random (MNAR), missing at random (MAR), and missing completely at random (MCAR). Little's MCAR test will be applied to identify if the characteristics of the missing variable are (Little, 1988). For the other two types, we will make use of the tests for interactions between observed variables. If a significant interaction exists, that will be treated as MNAR data. Missing samples will be imputed using previously suggested well-known approaches suitable for the category of the missing variable (Sarker, Tyburski, Rahman, et al., 2016).

14.9 Demographic and Baseline Characteristics

Descriptive summaries of the distribution of continuous baseline variables will be presented with percentiles (median, 25th and 75th percentiles), and with mean and standard deviation. Categorical variables will be summarized in terms of frequencies and percentages.

14.10 Safety Analysis

Not applicable, as no treatment/intervention is being provided for this study.

15.0 REGULATORY COMPLIANCE, REPORTING and MONITORING

15.1 Statement of Compliance

This study will be conducted in accordance with the current version of the protocol, in full conformity with the ethical principles outlined in the Declaration of Helsinki, the Protection of Human Subjects described in the International Council for Harmonization Good Clinical Practice (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 Investigators 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 quality assurance tool.

15.2 Institutional Review Board Approval

Prior to initiating the study, participating site investigators will obtain written approval from the Ethics Review Committee (ERC) or Institutional Review Board (IRB) to conduct the study at their respective site, which will include approval of the study protocol. If changes to the study protocol become necessary, protocol amendments will be submitted in writing by the investigators for IRB approval prior to implementation. In addition, IRBs will approve all consent forms, recruitment materials, and any materials given to the participant, and any changes made to these documents throughout study implementation. 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 Principal 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 (UP) involving risk to study participants will be promptly reported to and reviewed by the IRB of record, according to its usual procedures.

The Kaiser Permanente Northern California Institutional Review Board will be the single IRB of record for the protocol and will provide study oversight in accordance with 45 CFR 46. Participating institutions will agree to rely on Kaiser IRB and will enter into reliance/authorization agreements for Protocol CTN-0084-A2. Kaiser IRB will follow written procedures for reporting its findings and actions to appropriate officials at each participating institution.

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 approved by Kaiser IRB. Prior to initial submission to the IRB and with each subsequent consent revision, the consent form must be sent to the Lead Node 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(b), 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. The site must maintain the electronically signed informed consent for every participant on a secure server located at Kaiser that is in compliance with all applicable IRB and institutional policies and that is accessible to the study monitors. Every study participant should be given a copy of the signed consent form.

During the informed consent process, research staff will explain the study to the potential participant by phone/video and provide the potential participant with 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 consent form and ask questions prior to signing. 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 will consent by providing an electronic date and signature. The person obtaining consent and a witness, if required by the IRB of record, will also electronically 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 Human Subjects Protection 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. 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. The study site will be responsible for maintaining electronically signed consent forms as source documents for quality assurance review and regulatory compliance.

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 study 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 or the participant.

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

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, 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 for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as denoted in Section 15.11.

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. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

15.5.2 Health Insurance Portability and Accountability Act (HIPAA)

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

15.6 Investigator Assurances

The site must have on file a Federalwide 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 in alignment with 45 CFR

46, Subpart A, with documentation sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103). Prior to initiating the study, the principal investigator at the study site will sign a protocol signature page and investigator agreement, providing assurances that the study will be performed according to the standards stipulated therein.

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

Qualified node personnel (Node QA monitors) or another designated party will provide site management for each site during the trial. Node QA staff or other designated party(ies) will audit source documentation, including electronic case report forms (eCRFs), informed consent forms and HIPAA forms. Node QA monitors will examine whether study procedures are conducted appropriately, and that the study data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulations. This will take place as specified by the local protocol team, node PI(s) or Lead Node and will occur as often as needed to help prevent, detect, and correct problems at the study site. 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. Reports will be prepared following the site visit (may be conducted remotely as appropriate) and sent to the Lead Team, Node Principal Investigator(s), and site Principal Investigator. Details of the node QA, and data monitoring are found in Module 10 of the study Manual of Operating Procedures.

15.8 Inclusion of Women and Minorities

The study site will aim and take steps to enroll a diverse study population. We are targeting approximately 50% female and 40% minority. If difficulty is encountered in recruiting an adequate number of women and/or minorities, the difficulties involved in recruitment will be discussed in national conference calls and/or face-to-face meetings, encouraging such strategies as linkages with medical sites and or treatment programs that serve a large number of women and/or minorities, advertising in newspapers or radio stations with a high female/minority readership/listening audience, etc.

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 incarcerated or otherwise meets the 45 CFR 46 Part C definition of a prisoner during the course of the study, and the relevant research proposal was not reviewed and approved by the Kaiser IRB in accordance with the requirements for research

involving prisoners under Subpart C of 45 CFR 46, the investigator must promptly notify the Kaiser IRB. All research interactions and interventions with, and obtaining identifiable private information about, the participant must be suspended immediately.

15.10 Regulatory Files

The regulatory files will contain all required regulatory documents, study-specific documents, and important communications. Regulatory files will be checked at the 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., electronic case report forms, source documents, signed consent forms, 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 from these parties 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 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 clinical research practice guidelines and may perform quality assurance audits for protocol compliance. The Lead Investigators and authorized staff from the Health Systems and Northeast Nodes; 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

The 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, Ethics Review Committee or Institutional Review Board correspondence and approved consent form and signed participant consent forms. As part of participating in a NIDA-sponsored study, the site will permit authorized representatives from NIDA and regulatory agencies to examine (and when permitted by law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source documents include <u>all</u> recordings of observations or notations of clinical activities and any 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.

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 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

Any departure from procedures and requirements outlined in the protocol will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. The site will be responsible for developing corrective action plans for both major and minor deviations as appropriate. Those corrective action plans may be reviewed/approved by the Lead Node and Kaiser IRB as needed. All protocol deviations will be monitored at the 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. The Lead Investigators must be contacted immediately if an unqualified or ineligible participant is randomized into the study.

Additionally, the 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. The site 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

The Lead Investigators (LI) may appoint a Study Clinician (PhD, PsyD) for this study, who will review or provide consultation for each reportable safety event as needed. These reviews will include an assessment of the possible relatedness of the event to the study intervention or other study procedures. The Study Clinician will also provide advice for decisions to exclude, refer, or withdraw participants as required. The Lead Investigators, along with input from the Study Clinicians, will determine which safety events require expedited reporting to NIDA and regulatory authorities. All events that are serious, related and unexpected, or that place subjects at greater risk of harm will be promptly reported to Kaiser IRB (IRB of Record), as outlined in KPNC IRB guidance (policy # N-CRSP HRP 071). The study staff will be trained to monitor for and report Safety Events. See local SOP safety plan for more details.

15.16.1Data and Safety Monitoring Board (DSMB)

As this is a minimal risk study and no safety analysis will be performed (and no events are anticipated), an independent CTN DSMB will not be convened for this study. Instead, a Protocol Review Board (PRB) approved the protocol prior to implementation (January 21, 2020). As no data are being collected by the Data and Statistics Center (DSC), no annual review of accumulating data will occur. In the unlikely event that a safety issue arises, the safety events that are specified for reporting to Kaiser IRB will be reported following KPNC IRB's reporting policies.

15.16.2 Safety Monitor/Medical Monitor

Detailed Safety Monitoring will not occur via the Lead Node, due to the minimal risk nature of this study. Kaiser IRB will be responsible for reviewing all safety events reported, should there be any. All safety events that occur will be reviewed by the study team on an approximately weekly basis as part of the study operations meeting to observe trends or unusual events. Although not anticipated, if a death occurs it will be reviewed immediately. Procedures will be developed to identify notification paths to the Lead Investigators, sponsor, and all study team members. Safety events will be reported to Kaiser IRB in accordance with their reporting policies.

The Lead Investigators will in turn report safety events to the sponsor on an as needed basis (at least annually).

15.16.3 Safety Events

Standard definitions for safety events, their identification, and relationship to study and processing are described in Appendix A.

Safety events may be elicited at baseline or spontaneously reported by the study participants at any time during participation in the study.

We will only collect safety events related to suicidal ideation and death.

The Study Clinician will review each safety event as it occurs, and details will be recorded in a secure database. Safety events requiring reporting to the Kaiser IRB will be completed in accordance with Kaiser IRB's policies and procedures. Any death occurring during the study or comes to the attention of the study staff during the protocol-defined follow-up period will be reviewed with the Study Clinician and Principal Investigator(s) and will be reported to the Kaiser IRB promptly if unanticipated and possibly related to the study or otherwise at time of annual review (See Appendix A for more details).

The NIDA Program Officer must be informed of any death occurring during the study or comes to the attention of the study staff during the protocol-defined follow-up period. This report is made to NIDA regardless of whether the death was study related or unanticipated.

16.0 DATA MANAGEMENT

16.1 Design and Development

Screening, baseline, and follow-up assessments will be collected via REDCap and stored on Dartmouth College's secure servers. REDCap is a widely used, secure platform for administering assessments in clinical trials. The Lead Node will be responsible for programming all the assessments, the development and validation of study database, and ensuring data integrity and security. Since many of the proposed assessments are already developed for use in REDCap, programming time should be minimal. The Structured Clinical Interview for DSM-5 (SCID-5) will be collected via TeleSage™'s electronic version called the NetSCID-5, which is fully licensed by the American Psychiatric Association. The NetSCID has been validated (Brodey, First, Linthicum, Haman, Sasiela, & Ayer, 2016). The NetSCID is HIPAA-compliant, and data is maintained on a secure, encrypted, and geo-redundant server. At the end of the study, all data collected on the TeleSage™ platform and stored on their server(s) will be securely transferred to Dartmouth's server and expunged from TeleSage™'s server(s). TeleSage™ has the capability to allow for customization only modules relevant for this study will be selected, programming time should be minimal.

The digital health technologies data will be collected by self-report EMAs via smartphone, smartwatch and smartphone sensors, and by social media (for those who consent). Data collected via smartphone and smartwatch (sensor and EMAs) will be encrypted and securely transferred to a secure database housed at the Research Computing Department at Dartmouth College. Social media data will be downloaded by the participant directly from the social media platform to a secure server using a remote desktop at the beginning of the study and at the end of the study. All social media data will be securely stored on an encrypted server at the Williamson Translational Research Building in the Biomedical Data Science Department at Dartmouth College. The EHR and medical claims data will be encrypted and securely transferred to a secure database housed at the Geisel School of Medicine at Dartmouth.

The data management responsibilities of the site will be specified by the Lead Node and outlined in the Data Management section of the MOP.

16.2 Data Center Responsibilities

The Lead Node will 1) develop a data management plan and will conduct data management activities in accordance with that plan, 2) provide final guided source documents and eCRFs (guided source documents for Screening, Baseline, and Follow-up only; eCRFs for all assessments) for the collection of all data required by the study, 3) develop data dictionaries for each eCRF and EMA that will comprehensively define each data element, 4) conduct ongoing data monitoring activities on study data from the site, 5) monitor any preliminary analysis data cleaning activities as needed, and 6) rigorously monitor final study data cleaning.

16.3 Data Collection

The data collection process for screening, baseline, and follow-up assessments consists of direct data entry at the study site into the REDCap application or TeleSage™'s electronic version of the SCID-5 (NetSCID-5) (collected at baseline only). In the unlikely event that REDCap or NetSCID-5 is not available, the site will reschedule the study appointment to a time when the electronic systems are available. Data entry into the REDCap system should be completed according to the instructions provided and project specific training. 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.

Digital health data will be collected by self-report EMAs via smartphone, smartwatch and smartphone sensors, and by social media (for those who consent). Data collected via smartphone and smartwatch (sensor and EMAs) will be encrypted and securely transferred to a secure database housed at the Research Computing Department at Dartmouth College. Social media data will be downloaded by the participant directly from the social media platform to a secure server using a remote desktop at the beginning of the study and at the end of the study. All social media data will be securely stored on an encrypted server at the Williamson Translational Research Building in the Biomedical Data Science Department at Dartmouth College. The EHR and medical claims data (limited data set) will be encrypted and securely transferred to a secure database house at the Geisel School of Medicine at Dartmouth.

16.4 Data Acquisition and Entry

For screening, baseline, and follow-up assessments, electronic data will be directly entered into REDCap by the research staff. The data is written to a file on the REDCap secure web server or TeleSage™ NetSCID-5 server, and data can only be accessed by logging in with a REDCap account or TeleSage™ NetSCID-5 account.

Digital health data will be collected by self-report EMAs via smartphone, smartwatch and smartphone sensors, and by social media (for those who consent). Data collected via smartphone and smartwatch (sensor and EMAs) will be encrypted and securely transferred to a secure database housed at the Research Computing Department at Dartmouth College. Social media data will be downloaded by the participant directly from the social media platform to a secure server using a remote desktop at the beginning of the study and at the end of the study. All social media data will be securely stored on an encrypted server at the Williamson Translational Research Building in the Biomedical Data Science Department at Dartmouth College. The EHR and medical claims data as a limited dataset will be encrypted and securely transferred to a secure database house at the Geisel School of Medicine at Dartmouth.

16.5 Data Editing

For the screening, baseline, and follow-up assessments completed data will be entered directly into REDCap and TeleSage™ NetSCID-5. Validation checks will be programmed within forms to ensure data is complete when collected. Photos of urine drug screen results will be uploaded and then results will be manually entered into REDCap. The Local Node will be responsible for ensuring accuracy of data entered into REDCap from the photos (UDS source documents). All data downloads and reports will be run by the Local Node on a regular basis to identify incomplete or inaccurate data. The site will be notified to resolve data inconsistencies and errors.

Digital health data will be collected passively via smartwatch and smartphone sensors and participants will be prompted to answer EMA questions and self-initiated EMAs via smartphone. In addition, for those who consent to the optional social media component, social media data will be retroactively downloaded by the participant directly from the social media platform to a secure server using a remote desktop at the beginning of the study and at the end of the study. All data will be collected via sensor or self-report, therefore, there will be no data editing. However, reports will be run on a regular basis on EMA and sensor data to ensure the smartwatches and smartphones are transmitting data.

16.6 Data Transfer/Lock

De-identified data will be made available by request from one of the Lead Nodes and with the approval of both PIs. This approach has been employed successfully before with CTN-0072 and is also the approach of CTN-0084. We employ this model because of potential concerns with privacy and re-identification. The study is recruiting from substance use treatment

programs from within a single health system, is only recruiting ~50 (if recruitment is faster than anticipated, we will recruit up to 75) patients, and has a brief recruitment time period. The number of some participants, particularly in the older age range, may be very small, further raising the concern for re-identification. The data collected also reflect very detailed data about participants' daily lives.

16.6.1 Data Training

The training plan for site staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, participant compensation via gift card, the use of the REDCap data collection application, the use of the TeleSage™ data collection platform, the use of smartphone and smartwatch devices, use of Dartmouth app and Garmin Connect app, use of the study dashboard, and use of the payment system for participant compensation via reloadable debit card for the digital health data.

16.6.2 Data Quality Assurance

To address the issue of data entry quality, the Lead Node 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 PUBLICATIONS AND OTHER RIGHTS

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN. Considerations for ensuring confidentiality of any shared data are described in Section 15.5.

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 4.0 of the protocol and agree to conduct this clinical study in accordance with the design and provisions specified therein.

- I agree to follow the protocol as written except in cases where necessary to protect the safety, rights, or welfare of a participant, an alteration is required, and the sponsor and IRB have been notified prior to the action.

- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.

- I agree to personally conduct or supervise this investigation at this site and to ensure that all site staff assisting in the conduct of this study are adequately and appropriately trained to implement this version of the protocol and that they are qualified to meet the responsibilities to which they have been assigned.

- I agree to comply with all the applicable federal, state, and local regulations regarding the obligations of clinical investigators as required by the Department of Health and Human Services (DHHS), the state, and the IRB.

SITE'S PRINCIPAL INVESTIGATOR

Printed Name		**Signature**		**Date**

Clinical Site Name		
Node Affiliation		

19.0 REFERENCES

Asch, D. A., Muller, R. W., & Volpp, K. G. (2012). Automated hovering in health care--watching over the 5000 hours. *New England Journal of Medicine, 367*(1), 1-3. doi: 10.1056/NEJMp1203869

Barnett, I., Torous, J., Staples, P., Sandoval, L., Keshavan, M., & Onnela, J. P. (2018). Relapse prediction in schizophrenia through digital phenotyping: A pilot study. *Neuropsychopharmacology*. doi: 10.1038/s41386-018-0030-z

Brodey, B.B., First, M., Linthicum, J., Haman, K., Saseila, J.W., & Ayer, D. (2016). Validation of the NetSCID: an automated web-based adaptive version of the SCID. *Comprehensive Psychiatry, 66,* 67-70. doi:10.1016/j.comppsych.2015.10.005

Brownstein, J. S., Freifeld, C. C., & Madoff, L. C. (2009). Digital disease detection--harnessing the Web for public health surveillance. *New England Journal of Medicine, 360*(21), 2153-2155, 2157. doi: 10.1056/NEJMp0900702

Burns, M. N., Begale, M., Duffecy, J., Gergle, D., Karr, C. J., Giangrande, E., & Mohr, D. C. (2011). Harnessing context sensing to develop a mobile intervention for depression. *Journal of Medical Internet Research, 13*(3), e55. doi: 10.2196/jmir.1838

Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res, 28*(2), 193-213.

Center for Behavioral Health Statistics and Quality. (2017). 2018 National Survey on Drug Use and Health (NSDUH): CAI Specifications for Programming (English Version). Substance Abuse and Mental Health Services Administration, Rockville, MD.

Centers for Disease Control and Prevention (CDC). (2016). Surveillance for viral hepatitis- United States. Atlanta, GA: U.S. Department of Health and Human Services.

Centers for Disease Control and Prevention (CDC). (2017). New hepatitis C infections nearly tripled over five years [Press release]

Centers for Disease Control and Prevention (CDC). (2018). Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: National Center for Health Statistics.

Chang, K. C., Wang, J. D., Tang, H. P., Cheng, C. M., & Lin, C. Y. (2014). Psychometric evaluation, using Rasch analysis, of the WHOQOL-BREF in heroin-dependent people undergoing methadone maintenance treatment: further item validation. *Health Qual Life Outcomes, 12*, 148. doi: 10.1186/s12955-014-0148-6

Cheng, D., Bahadori, M. T., & Liu, Y. (2014). FBLG: a simple and effective approach for the temporal dependence discovery from time series data. *Proceedings of the 20th ACM SIGKDD international conference on knowledge discovery and data mining, 14*, 382-391.

Choudhury, M. D., Gamon, M., Counts, S., & Horvitz, E. (2013). *Predicting depression via social media.* Paper presented at the International AAAI Conference on Web and Social Media, North America.

Collins, L. M., & Graham, J. W. (2002). The effect of the timing and spacing of observations in longitudinal studies of tobacco and other drug use: temporal design considerations. *Drug Alcohol Depend, 68 Suppl 1*, S85-96. doi:10.1016/s0376-8716(02)00217-x

Connock, M., Juarez-Garcia, A., Jowett, S., Frew, E., Liu, Z., Taylor, R. J., . . . Taylor, R. S. (2007). Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health Technol Assess, 11*(9), 1-171, iii-iv.

Darden, W. R., & Perreault, W. D. (1976). Identifying interurban shoppers: multiproduct purchase patterns and segmentation profiles. *J Marketing Res, 13*(1), 51-60. doi: 10.2307/3150901

DeVito, E. E., Carroll, K. M., & Sofuoglu, M. (2016). Toward Refinement of Our Understanding of the Fundamental Nature of Addiction. *Biol Psychiatry, 80*(3), 172-173. doi: 10.1016/j.biopsych.2016.06.007

Dupouy, J., Palmaro, A., Fatseas, M., Auriacombe, M., Micallef, J., Oustric, S., & Lapeyre-Mestre, M. (2017). Mortality Associated With Time in and Out of Buprenorphine Treatment in

French Office-Based General Practice: A 7-Year Cohort Study. *Annals of Family Medicine, 15*(4), 355-358. doi:10.1370/afm.2098

Fiellin, D. A., Moore, B. A., Sullivan, L. E., Becker, W. C., Pantalon, M. V., Chawarski, M. C., . . . Schottenfeld, R. S. (2008). Long-term treatment with buprenorphine/naloxone in primary care: results at 2-5 years. *Am J Addict, 17*(2), 116-120. doi:10.1080/10550490701860971

First, M.B., Williams, J.B.W., Karg, R.S., and Spitzer, R.L. (2015) *Structured Clinical Interview for DSM-5 Research Version SCID-5-RV*. Washington, DC: American Psychiatric Association Publishing.

Freeman, L. K., & Gottfredson, N. C. (2018). Using ecological momentary assessment to assess the temporal relationship between sleep quality and cravings in individuals recovering from substance use disorders. *Addict Behav, 83*, 95-101. doi: 10.1016/j.addbeh.2017.11.001

Gustafson, D. H., McTavish, F. M., Chih, M. Y., Atwood, A. K., Johnson, R. A., Boyle, M. G., . . . Shah, D. (2014). A smartphone application to support recovery from alcoholism: a randomized clinical trial. *JAMA Psychiatry, 71*(5), 566-572. doi: 10.1001/jamapsychiatry.2013.4642

Hamilton, C.M., Strader, L.C., Pratt, J.G., Maiese, D., Hendershot, T., Kwok, R.K., . . . Haines, J. (2011). The PhenX Toolkit: Get the Most From Your Measures, *American Journal of Epidemiology*, *, Volume 174*(3), 253–260. doi:10.1093/aje/kwr193

Hartman, L., Barnes, E., Bachmann, L., Schafer, K., Lovato, J., & Files, D. C. (2016). Opiate injection-associated infective endocarditis in the Southeastern United States. *American Journal of the Medical Sciences, 352*(6), 603-608. doi: 10.1016/j.amjms.2016.08.010

Hernan, M. A., & Robins, J. M. (2006). Instruments for causal inference: an epidemiologist's dream? *Epidemiology, 17*(4), 360-372. doi: 10.1097/01.ede.0000222409.00878.37

Hsueh, P. S., Das, S., Maduri, C., & Kelly, K. (2018). Learning to Personalize from Practice: A Real World Evidence Approach of Care Plan Personalization based on Differential Patient Behavioral Responses in Care Management Records. *AMIA Annu Symp Proc, 2018*, 592-601.

Jain, S. H., Powers, B. W., Hawkins, J. B., & Brownstein, J. S. (2015a). The digital phenotype. *Nat Biotechnol, 33*(5), 462-463. doi: 10.1038/nbt.3223

Johnson, R. E., Jaffe, J. H., & Fudala, P. J. (1992). A controlled trial of buprenorphine treatment for opioid dependence. *The Journal of the American Medical Association, 267*(20), 2750-2755.

Katz, J. (2017, June 5, 2017). Drug deaths in American are rising faster than ever. *The New York Times*. Retrieved from https://www.nytimes.com/interactive/2017/06/05/upshot/opioid-epidemic-drug-overdose-deaths-are-rising-faster-than-ever.html

Kazemi, D. M., Borsari, B., Levine, M. J., & Dooley, B. (2017). Systematic review of surveillance by social media platforms for illicit drug use. *J Public Health (Oxf)*, 1-14. doi: 10.1093/pubmed/fdx020

Keeshin, S. W., & Feinberg, J. (2016). Endocarditis as a marker for new epidemics of injection drug use. *American Journal of the Medical Sciences, 352*(6), 609-614. doi: 10.1016/j.amjms.2016.10.002

Kim, S. J., Marsch, L. A., Brunette, M. F., & Dallery, J. (2017). Harnessing Facebook for Smoking Reduction and Cessation Interventions: Facebook User Engagement and Social Support Predict Smoking Reduction. *Journal of Medical Internet Research, 19*(5), e168. doi: 10.2196/jmir.6681

Kim, S. J., Marsch, L. A., Hancock, J. T., & Das, A. K. (2017). Scaling up research on drug abuse and addiction through social media big data. *Journal of Medical Internet Research, 19*(10), e353. doi: 10.2196/jmir.6426

Kim, S. J., Scherer, E. A., Metcalf, S. A., Sweeney, M. A., Wu, J., Gonzalez, O., . . . Marsch, L. A. (Under Review). Can we measure momentary changes in self-regulation: The development and validity of a novel momentary self-regulation scale. *Psychological Assessment*.

Kleinberg, S., & Hripcsak, G. (2011). A review of causal inference for biomedical informatics. *J Biomed Inform, 44*(6), 1102-1112. doi: 10.1016/j.jbi.2011.07.001

Kosinski, M., Stillwell, D., & Graepel, T. (2013). Private traits and attributes are predictable from digital records of human behavior. *Proceedings of the National Academy of Sciences of the United States of America, 110*(15), 5802-5805. doi: 10.1073/pnas.1218772110

Kraskov, A., Stogbauer, H., & Grassberger, P. (2004). Estimating mutual information. *Phys Rev E Stat Nonlin Soft Matter Phys, 69*(6 Pt 2), 066138. doi: 10.1103/PhysRevE.69.066138

Kuerbis, A., Reid, M. C., Lake, J. E., Glasner-Edwards, S., Jenkins, J., Liao, D., . . . Moore, A. A. (2019). Daily factors driving daily substance use and chronic pain among older adults with HIV: An exploratory study using ecological momentary assessment. *Alcohol, 77*, 31-39. doi: 10.1016/j.alcohol.2018.10.003

Ling, W., Charuvastra, C., Collins, J. F., Batki, S., Brown, L. S., Jr., Kintaudi, P., . . . Segal, D. (1998). Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction, 93*(4), 475-486. doi:10.1046/j.1360-0443.1998.9344753.x

Little, R. J. (1988). A test of missing completely at random for multivariate data with missing values. *Journal of the American Statistical Association, 83*, 119801202.

Lundberg, S. M., & Lee, S.-I. (2017). A unified approach to interpreting model predictions. *Advances in Neural Information Processing Systems*, 4765-4774.

Marsch, L. A. (2018a). Opportunities and needs in digital phenotyping. *Neuropsychopharmacology*. doi: 10.1038/s41386-018-0051-7

Marsch, L. A. (2018b). Opportunities and needs in digital phenotyping. *Neuropsychopharmacology, 43*(8), 1637-1638. doi: 10.1038/s41386-018-0051-7

Marsch, L. A., Lord, S. E., & Dallery, J. (2014). The state of the science of technology-based behavioral health care: An editorial. In L. A. Marsch, S. E. Lord, & J. Dallery (Eds.), *Behavioral Health Care and Technology: Using Science-Based Innovations to Transform Practice*: Oxford University Press.

McCarthy, D. E., Piasecki, T. M., Lawrence, D. L., Jorenby, D. E., Shiffman, S., & Baker, T. B. (2008). Psychological mediators of bupropion sustained-release treatment for smoking cessation. *Addiction, 103*(9), 1521-1533. doi: 10.1111/j.1360-0443.2008.02275.x

Mofsen, A. M., Rodebaugh, T. L., Nicol, G. E., Depp, C. A., Miller, J. P., & Lenze, E. J. (2019). When All Else Fails, Listen to the Patient: A Viewpoint on the Use of Ecological Momentary Assessment in Clinical Trials. *JMIR Ment Health, 6*(5), e11845. doi: 10.2196/11845

Naslund, J. A., Aschbrenner, K. A., Kim, S. J., McHugo, G. J., Unutzer, J., Bartels, S. J., & Marsch, L. A. (2017). Health behavior models for informing digital technology interventions for individuals with mental illness. *Psychiatric Rehabilitation Journal, 40*(3), 325-335. doi: 10.1037/prj0000246

Naslund, J. A., Kim, S. J., Aschbrenner, K. A., McCulloch, L. J., Brunette, M. F., Dallery, J., . . . Marsch, L. A. (2017). Systematic review of social media interventions for smoking cessation. *Addictive Behaviors, 73*, 81-93. doi: 10.1016/j.addbeh.2017.05.002

Nugent, N. R., Pendse, S. R., Schatten, H. T., & Armey, M. F. (2019). Innovations in Technology and Mechanisms of Change in Behavioral Interventions. *Behav Modif*, 145445519845603. doi: 10.1177/0145445519845603

Onnela, J. P., & Rauch, S. L. (2016). Harnessing Smartphone-Based Digital Phenotyping to Enhance Behavioral and Mental Health. *Neuropsychopharmacology, 41*(7), 1691-1696. doi: 10.1038/npp.2016.7

Patrick, S. W., Davis, M. M., Lehmann, C. U., & Cooper, W. O. (2015). Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. *Journal of Perinatology, 35*(8), 650-655. doi: 10.1038/jp.2015.36

Preston, K. L., Kowalczyk, W. J., Phillips, K. A., Jobes, M. L., Vahabzadeh, M., Lin, J. L., . . . Epstein, D. H. (2017). Context and craving during stressful events in the daily lives of drug-

dependent patients. *Psychopharmacology (Berl), 234*(17), 2631-2642. doi: 10.1007/s00213-017-4663-0

Preston, K. L., Kowalczyk, W. J., Phillips, K. A., Jobes, M. L., Vahabzadeh, M., Lin, J. L., . . . Epstein, D. H. (2018). Before and after: craving, mood, and background stress in the hours surrounding drug use and stressful events in patients with opioid-use disorder. *Psychopharmacology (Berl), 235*(9), 2713-2723. doi: 10.1007/s00213-018-4966-9

Rhyan, C. N. (2017). The potential societal benefit of eliminating opioid overdoses, deaths, and substance use disorders exceeds $95 billion per year (C. f. V. a. H. Care, Trans.). Washington, D.C.: Altarum.

Roos, C. R., & Witkiewitz, K. (2017). A contextual model of self-regulation change mechanisms among individuals with addictive disorders. *Clin Psychol Rev, 57*, 117-128. doi: 10.1016/j.cpr.2017.08.008

Rubin, D. B. (1974). Estimating causal effects of treatments in randomized and nonrandomized studies. *Journal of Educational Psychology, 66*(5), 688-701. doi: 10.1037/h0037350

Sarker, H., Tyburski, M., Rahman, M. M., Hovsepian, K., Sharmin, M., Epstein, D. H., . . . Kumar, S. (2016). Finding Significant Stress Episodes in a Discontinuous Time Series of Rapidly Varying Mobile Sensor Data. *Proc SIGCHI Conf Hum Factor Comput Syst, 2016*, 4489-4501. doi: 10.1145/2858036.2858218

Schuman-Olivier, Z., Weiss, R. D., Hoeppner, B. B., Borodovsky, J., & Albanese, M. J. (2014). Emerging adult age status predicts poor buprenorphine treatment retention. *J Subst Abuse Treat, 47*(3), 202-212. doi:10.1016/j.jsat.2014.04.006

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annual Review of Clinical Psychology, 4*, 1-32.

Simon, C. B., Tsui, J. I., Merrill, J. O., Adwell, A., Tamru, E., & Klein, J. W. (2017). Linking patients with buprenorphine treatment in primary care: Predictors of engagement. *Drug and Alcohol Dependence, 181*, 58-62. doi: 10.1016/j.drugalcdep.2017.09.017

Sordo, L., Barrio, G., Bravo, M. J., Indave, B. I., Degenhardt, L., Wiessing, L., . . . Pastor-Barriuso, R. (2017). Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *British Journal of Medicine, 357*, j1550. doi:10.1136/bmj.j1550

Spruijt-Metz, D., & Nilsen, W. (2014). Dynamic models of behavior for just-in-time adaptive interventions. *IEEE Pervasive Computing, 13*(3), 13-17.

Weinstein, Z. M., Kim, H. W., Cheng, D. M., Quinn, E., Hui, D., Labelle, C. T., . . . Samet, J. H. (2017). Long-term retention in office based opioid treatment with buprenorphine. *Journal of Substance Abuse Treatment, 74*, 65-70. doi: 10.1016/j.jsat.2016.12.010

Weiss, R. D., & Rao, V. (2017). The Prescription Opioid Addiction Treatment Study: What have we learned. *Drug and Alcohol Dependence, 173 Suppl 1*, S48-s54. doi:10.1016/j.drugalcdep.2016.12.001

20.0 APPENDIX A: SAFETY EVENT REPORTING AND PROCEDURES

The site's Principal Investigator is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified and trained study personnel to assess, report, and monitor adverse events.

Definition of Safety Events

This is a minimal risk study; therefore, no causally related Adverse Events (AE) or Severe Adverse Events (SAE) are anticipated and will not be captured. For the purposes of this protocol, safety reporting will be limited to reporting suicidal ideation and deaths only. These safety events will be captured on a Safety Event Log. The sites must follow local standard operating procedures for managing any medical or psychiatric emergencies.

As hospitalizations and overdoses of participants will be collected as data in this study, these are not considered safety events and will not be tracked on the Safety Event Log. In the event that a participant death is reported, the local team will report this to the KPNC IRB and to the study sponsor following the guidelines set forth (see the study Manual of Operating Procedures for more details).

Study staff will be trained to monitor and report all safety events on the Safety Event Log. The Log will be sent to the Lead Project Manager at least weekly, or stored on the shared drive to which all applicable study team members have access. If applicable, the Study Clinician and Lead Team will determine which safety events require reporting to KPNC IRB, NIDA CCTN and any other relevant regulatory authorities.

The study is a feasibility study, which involves three phone interviews (two baseline and one 12-week post-EMA start follow-up), and collection of active and passive digital health data (EMA, smartphone and smartwatch sensor data, and EHR and medical claims data). This study is not a clinical trial. Therefore, study safety events are expected to be extremely rare.

Identifying Safety Events

Safety events may be elicited at baseline during the NetSCID-5 assessment or spontaneously reported to study staff at any visit following consent. Examples of spontaneously reported (unsolicited) safety events include:

- Receiving an unsolicited remark or complaint from the participant or a friend, family member or other person about the participant's intent to harm themselves.
- Information may be discovered after the participant spontaneously reports a complaint (e.g., plans to attempt suicide).

When safety events are reported, study staff will obtain as much information as possible about the reported event to complete documentation of the Safety Event Log and will consult with the Study Clinician and Lead Investigators as warranted. Safety event assessment will begin with participant consent and follow-up will continue until resolution, stabilization or study end. All reported safety events will be followed until resolution or stabilization but will cease at the end of the 12-week active window for participants in the study.

Documenting Safety Events

Any safety event that occurs after consent will be documented on the designated Safety Event Log. All safety events will be brought to the attention of the Lead Team and reviewed on the weekly study call.

Suicidal ideation will not be captured as AEs or SAEs but instead will be reported on the Safety Event Log described below.

Suicidal ideation may be reported via the NetSCID-5 assessment at baseline or via spontaneous report from the participant. In the event of suicidal ideation and behavior reporting, participants may need additional and immediate follow-up from the Study Clinician. Refer to the Critical Incident SOP for further details.

Monitoring Safety Events

Quality Assurance (QA) monitors will routinely review study records for any unreported safety events and ensure these events are promptly reported to the Lead Investigators, and to the IRB of record, per IRB reporting requirements. The monitor will document safety related information in the Site Visit Report. Any unreported safety events identified by monitors will be reported as protocol deviations. To ensure timely identification and reporting of future safety events, study staff education, re-training, or another appropriate corrective action plan may be implemented when unreported safety events are discovered. See Module 10 of the study Manual of Operating Procedures for specific guidelines on monitoring processes.

Reporting Safety Events

What to report?	• This study has no reportable AEs or SAEs. Only safety events (i.e., suicidality and deaths) will be recorded in the Safety Event Log. If required, study staff will report safety events to the IRB of Record in accordance with the IRB's policies and procedures.
When to report?	• Research staff will consult with Study Clinician about whenever suicidality is reported or insinuated. Safety events are to be reported on the Safety Event Log within 24 hours of event, and all entries will be reviewed by Study Clinician or Local PM within 48 hours of the entry. Research staff should follow the guidelines of KPNC IRB to determine the reporting requirements of reportable safety events as described in Section 9.8.1.
How to report?	• Safety events are reported via the Safety Event Log. • The Log must be completed with as much relevant information as is available at the time of study staff awareness of the event. • A Study Clinician is responsible for reviewing all safety events and may also request additional and updated information, as well as request follow up actions. • Study staff should follow all instructions in the Critical Incident SOP. • The Local PM will email the Log to the Lead PM weekly (i.e., final business day) or upload it to the secure shared drive to which all appropriate study team members have access.

How will the event be monitored?	• Study staff will follow local procedures outlined in the Critical Incident SOP. • The Study Clinician will report to the Local PM on the outcome of the assessment and will complete the Safety Event Log as needed. • The Lead Team will report study safety events to NIDA CCTN on an as-needed basis (at least annually). The study sponsor retains the authority to suspend additional enrollment and participation for the entire study as applicable.

The Lead Investigators are responsible for reviewing all safety events and may also request additional and updated information. The Lead Investigators, along with input from the Study Clinicians, will determine which safety events require expedited reporting to the IRB, NIDA CCTN, and regulatory authorities. All events that are serious, related, unexpected, or that place subjects at greater risk of harm will be promptly reported to Kaiser IRB (IRB of record), as outlined in KPNC IRB guidance (policy # N-CRSP HRP 071).

If information related to the safety event is not completed when it is initially reported or if new information becomes available after the Safety Event Log is submitted, a follow-up report (containing any additional or updated information) must be submitted as soon as possible, but at most within 14 days after the study staff receives the updated information.

The anticipated safety events for this study (i.e., suicidal ideation) are *not* required to be reported to the KPNC IRB unless there is evidence that they are causally related to the research procedures. If a site is ever unsure whether an event should be reported to the IRB, they should discuss with the KPNC IRB.

While unlikely to occur in this low-risk study, unanticipated study-related problems involving risks to subjects or others must be reported via KPNC IRB's Reportable New Information Form, with supporting documentation as soon as possible, but no later than 5 business days of becoming aware of the event and deaths unanticipated and possibly related to the study must be reported within 24 hours (see the study Manual of Operating Procedures for a description of these events and reporting requirements).

All events should be followed up to resolution.

Sponsor's Role in Safety Management Procedures of Safety Events

The Sponsor or designee will not be involved in safety management procedures for this study. The Study Clinician is responsible for reviewing all Safety Events. The Lead Investigators and designees will also be promptly informed of all reported Safety Events, for example via email. The Lead Investigators or designee will report to external parties as required, including the sponsor and IRB of record.

Reporting Safety Events to the Data and Safety Monitoring Board

There will be no DSMB for this study.

Participant Discontinuation Due to a Safety Event

There may be some situations in which a safety event requires that a participant be discontinued from study participation. Participants may be discontinued from the study in the following situation(s):

- Participant's condition has deteriorated during the course of the study:
  - Emergence of psychosis, suicidal ideation, overdose, severe cognitive impairment, dangerous criminal behaviors; or
  - New onset of psychiatric or medical conditions requiring intervention that preclude continued study participation.

The Study Clinician, in collaboration with the Site PI, should consult with the Lead Team in making the decision to withdraw a participant from the study.

21.0 APPENDIX B: DATA AND SAFETY MONITORING PLAN

1.0 BRIEF STUDY OVERVIEW

Across the U.S., the prevalence of opioid use disorder (OUD) and the rates of opioid overdoses have risen precipitously in recent years. Drug overdose is being called a “modern plague” (Katz, 2017) and is now the leading cause of death of Americans under age 50, having surpassed peak death rates from gun violence, HIV, and car crashes (Centers for Disease Control and Prevention (CDC), 2018; Katz, 2017). This dramatic spike in OUD has also been accompanied by marked increases in injection-related infections (including infective endocarditis and Hepatitis C) (Centers for Disease Control and Prevention (CDC), 2016, 2017; Hartman et al., 2016; Keeshin & Feinberg, 2016), babies born with Neonatal Opioid Withdrawal Syndrome (Patrick, Davis, Lehmann, & Cooper, 2015) and healthcare and criminal justice costs (Rhyan, 2017).

Several effective medication-assisted treatments for OUDs exist. Treatment models for OUDs that include buprenorphine medication are among the most effective treatment models. Buprenorphine treatment for OUD has been shown to greatly increase opioid abstinence, reduce HIV/infectious disease risk behavior, and criminality. Greater retention in such treatment models are associated with the most positive treatment outcomes (Connock et al., 2007; Johnson, Jaffe, & Fudala, 1992; Ling et al., 1998; Sordo et al., 2017a). However, given the chronic relapsing nature of the disease of addiction, many individuals continue to engage in opioid use during treatment. Further, many individuals who enter buprenorphine treatment do not consistently take their medication or remain engaged in treatment – typically resulting in continued opioid use (which is accompanied by risk of overdose) (Fiellin et al., 2008; Schuman-Olivier, Weiss, Hoeppner, Borodovsky, & Albanese, 2014) Although many factors have been shown to predict non-adherence in substance use disorder treatment (Simon et al., 2017; Weinstein et al., 2017) (including stress, mental health comorbidities, and continued exposure to high risk social networks or contexts), most studies have examined a small set of potential moderators or mediators of outcomes in treatment for OUD and may lead to over-simplified accounts of treatment non-adherence.

More frequent and longer assessment of moderators, mediators, and outcome(s) are necessary to elucidate the temporal dynamics between changes in specific mechanisms and treatment non-adherence behavior (Collins & Graham, 2002). Examining a broad array of factors impacting treatment non-adherence at multiple levels of analysis will enable a more comprehensive picture and will increase our ability to develop more impactful interventions for OUD.

Advances in **digital technologies and data analytics** have created new opportunities to assess and modify health behavior and thus accelerate the ability of science to understand and contribute to improved health behavior and health outcomes. Given the ubiquity of access to digital technologies worldwide, digital tools allow for the examination of health behavior and clinical trajectories within-individuals through intensive collection of individual-level, real-time data collected via surveys on mobile device (referred to as Ecological Momentary Assessment [EMA]), wearable sensors (on smartphones and/or smartwatches), and mapping digital footprints. Digitally-derived data allow for the development of dynamic models of health behavior to understand behavior in real-time and in response to changing environmental, social, physiological, and intrapersonal factors (Naslund et al., 2017; Spruijt-Metz, 2014). As applied to persons with OUD, digital data that offers ongoing assessment of behavior as individuals live their daily lives can help us better understand the trajectory of clinically important behaviors (e.g., treatment retention; medication adherence over time) and identify fluctuating contextual factors that greatly influence such behaviors, (e.g., patterns leading to relapse or treatment dropout).

2.0 OVERSIGHT OF CLINICAL RESPONSIBILITIES

A. Site Principal Investigator

The Site 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 adverse events.

All reportable Safety Events occurring during the course of the study will be collected, documented, and reported by the investigator or designee to the Protocol.

The occurrence of Safety Events will be assessed as appropriate. All Safety Events will be followed up to resolution as described in Appendix A of the Protocol.

Most reportable Safety Events are required to be reported to the Kaiser IRB within 5 business days of the site staff becoming aware of the event. However, some reportable Safety Events (including death and unauthorized use or disclosure of confidential subject information or KP information) are required to be reported to the Kaiser IRB within 1 business day of site's knowledge of the event (see the study Manual of Operating Procedures for more detailed information).

B. Safety Monitor/Medical Monitor

Since this is a minimal risk study, a Safety Monitor/Medical Monitor will not be appointed. Safety Events will be reported to the Study Clinician and Lead Investigators who will, in turn, report to applicable regulatory bodies, including the IRB of Record.

C. Data and Safety Monitoring Board (DSMB)

Not applicable as there will be no DSMB.

D. Quality Assurance (QA) Monitoring

The monitoring of the study site will be conducted on a regular basis using the QA Monitors. Investigators will host periodic visits for the monitors (may be conducted remotely). 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 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 study staff to identify issues and re-train as needed to enhance research quality.

QA Monitors site visit reports will be prepared following each site visit, as applicable. These reports are sent to those entities required of them by the study Lead Team, Node Principal Investigator(s), and site Principal Investigator.

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/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

A designated and qualified individual at the site will evaluate all pertinent screening and baseline assessments prior to participant enrollment to ensure that the participant is eligible and safe to enter the study. Safety Events will be collected if elicited at baseline or spontaneously reported by participants during their participation in the study. Individuals who experience a Safety Event that compromises safe participation in a study will be discontinued from further participation and provided referrals for other treatment or to specialized care as needed.

Pregnancy

As there is no medication intervention, pregnancy will not be followed within the context of this study.

Study Specific Risks

Suicidal ideation is a possible risk. Other potential risks are low due to the data not being monitored in real time but being sent directly to a data warehouse. Participants will be told in case of immediate crisis or emergency, they should call 911 or a medical provider. The low potential risks may include*:*

- **Risk from EMAs:** The types of risk associated with the data collected include possible fatigue, frustration, or the discussion of sensitive or personal information. If participants do not wish to answer particular mobile surveys, they may elect not to do so, and may continue in the remainder of the study without penalty. Additionally, participants may be concerned about confidentiality when using the smartphone to transmit EMA responses, even with data encryption and secure cloud-based data transfer. They may also be worried about prompts they receive on their mobile device designed to remind them to complete the EMA questions.
    - To protect against risk of fatigue and frustration, we have intentionally developed the EMAs to be brief (approximately 10 mins to complete). Anyone who experiences discomfort with the sensitive or personal EMA questions, can either elect not to answer the questions or are advised that they can discontinue their participation at any point without penalty. Finally, to protect against concerns that others may see when a participant receives an EMA prompt, the content of the prompt will be intentionally vague. The prompts will be designed to be meaningful to the participant, but they will not include specific references to study participation.
- **Risk from mobile sensing:** Participants might experience slight initial discomfort while wearing the smartwatch, such as minor skin irritations. As with any electrical device, the sensors can theoretically cause electric shocks. Electric shocks can be a health concern with certain health conditions (e.g., heart conditions that require a pacemaker). Additionally, participants could have privacy concerns regarding mobile sensing (smartwatch or smartphone).
    - Although slight discomfort is possible from wearing the smartwatch, the smartwatch

has been used in multiple field studies with many participants, and no significant skin irritation has been reported. Therefore, we expect the severity of the discomfort and irritation of wearing the smartwatch to be minimal. If irritation persists to a point where the participant no longer wishes to participate, any irritation is reversible once the participant removes the smartwatch.

- While electrical devices do introduce the risk of electric shocks, the probability of a participant experiencing even minor electrical shocks is negligible. High impedance circuitry is used to limit current flow, even in the case of external events (e.g., through physical breaking of the sensor board or shorting of the battery leads). All sensors in the smartwatch are commonly used in mobile phones and other activity monitors and pose minimal risk to participants. Previous studies with wristband sensors have indicated that after a brief adjustment period, the majority of the participants adjusted to wearing the bands and did not find them to be intrusive or restraining. We expect that the smartwatch, which have precedent of prior use in a research study or have otherwise been designed for everyday wear, will elicit similar acceptability among the participants in this study.

- Regarding privacy concerns, participants' contact information will be linked to their study data via a code. Participants will be informed of their rights to terminate their participation in the study at any time. Participants will also be informed of their rights to remove the smartwatch and/or not carry their smartphone if they so choose, if they do not wish to be tracked.

- **Risk from social media data:** We will ask participants to provide us with information they post to their social media (e.g., Facebook, Instagram, and Twitter). We will evaluate each participant's posted images, captions, and comments. Participants may feel uncomfortable sharing their social media communications.

  - We recognize that some participants may not have a social media account, and some may not want to share their social media data with researchers. Participants can choose not to share this information (consent to share social media data will be separate consent line(s) on the consent form) and they can still be eligible to participate in other parts of the study. Note that we will not directly collect data from friends/members of participants' social networks but will only ask participants if they provide permission for us to learn about their relationships with their social network members via information participants post on their own social media. Additionally, we will never publish social media text quotations from participants or present participants' information in ways that could potentially be identifiable.

3.0 DATA MANAGEMENT PROCEDURES

For the screening, baseline, and follow-up assessments, electronic data will be entered into REDCap application and the SCID-5 assessment will be entered into TeleSage™ NetSCID-5 by the research staff during the assessment. The data is written to a file on the REDCap and TeleSage™ NetSCID-5 secure web servers, and data can only be accessed by logging in with a REDCap or TeleSage™ NetSCID-5 account. These electronic data capture systems will meet the guidelines and regulations surrounding the use of computerized systems in clinical trials.

For the digital health technology, all data will be electronically captured either via study participant self-report or passively via smartwatch and smartphone sensors. The sensor and EMA data will be encrypted and securely transferred to a secure database. Social media data will be downloaded by the participant (from those who consent) directly from the social media site to the study team's server using a remote desktop and stored on a secure encrypted server housed at

the Williamson Translational Research Building in the Biomedical Data Science Department at Dartmouth College. The EHR and medical claims data will be encrypted and securely transferred to a secure database. Only research team members will have access to the secure servers housing the digital study data.

4.0 DATA AND STATISTICS CENTER RESPONSIBILITIES

The Lead Node will 1) develop a data management plan and will conduct data management activities in accordance with that plan, 2) provide final guided source documents and eCRFs (guided source documents for Screening, Baseline, and Follow-up only; eCRFs for all assessments) for the collection of all data required by the study, 3) develop data dictionaries for each eCRF and EMA that will comprehensively define each data element, 4) conduct ongoing data monitoring activities on study data from the site, 5) monitor any preliminary analysis data cleaning activities as needed, and 6) rigorously monitor final study data cleaning.

5.0 DATA COLLECTION AND ENTRY

Data will be collected at the study site via digital forms in the REDCap system and TeleSage™ NetSCID-5 system. In the event that REDCap or and TeleSage™ NetSCID-5 is not available, the research staff will reschedule the study appointment to a time when the electronic systems are available. Data will be entered into REDCap and TeleSage™ NetSCID-5 in accordance with the instructions provided during protocol-specific training and guidelines established by the Lead Node. Data entry into the eCRFs is performed by authorized individuals. In some situations, data collected on source documents will not be entered into REDCap, but when it is entered, it will follow the guidelines stated above.

The project manager for the site is responsible for ensuring the site maintains accurate, complete, and up-to-date research records.

Digital health data will be collected by self-report EMAs via smartphone, smartwatch and smartphone sensors, and by social media (for those who consent). All data will be collected electronically. Data collected via smartphone and smartwatch (sensor and EMAs) will be encrypted and securely transferred to a secure database housed at the Research Computing Department at Dartmouth College. Social media data will be downloaded by the participant directly from the social media platform to a secure server using a remote desktop at the beginning of the study and at the end of the study (if consented). All social media data will be securely stored on an encrypted server at the Williamson Translational Research Building in the Biomedical Data Science Department at Dartmouth College. The EHR and medical claims limited dataset will be encrypted and securely transferred to a secure database house at the Geisel School of Medicine at Dartmouth.

6.0 DATA MONITORING, CLEANING AND EDITING

eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and forms are available to site at all times in REDCap and TeleSage™ NetSCID-5. These reports will be monitored regularly by the Local Node.

Digital health data will be collected passively via smartwatch and smartphone sensors and participants will be prompted to answer EMA questions via smartphone. In addition, for those who consent to the optional social media component, social media data will be retroactively downloaded by the participant directly from the social media platform to a secure server using a remote desktop at the beginning of the study and at the end of the study. All data will be collected via sensor or self-report, therefore, there will be no data editing. However, reports will be run on a regular basis on EMA and sensor data to ensure the smartwatches and smartphones are transmitting data.

Information on recruitment, availability of primary outcome, treatment exposure, attendance at long term follow-up visits, regulatory status, and data quality, may be generated approximately monthly, and will be made available to the site, the corresponding Node, the Lead Investigators, and NIDA CCTN, to monitor the site's progress on the study.

7.0 DATABASE LOCK AND TRANSFER

At the conclusion of data collection for the study, the Lead Node will perform final data cleaning activities and the study database will be "locked" from further modification. The final analysis will be completed by the Lead Investigators. De-identified data will be made available by request from one of the Lead Nodes and with the approval of both PIs. This approach has been employed successfully before with CTN-0072 and is also the approach of CTN-0084. We employ this model because of potential concerns with privacy and re-identification. The study is recruiting from substance use treatment programs from within a single health system, is only recruiting ~50 (if recruitment is faster than anticipated, we will recruit up to 75) patients, and has a brief recruitment time period. The number of some participants, particularly in the older age range, may be very small, further raising the concern for re-identification. The data collected also reflect very detailed data about participants' daily lives.

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