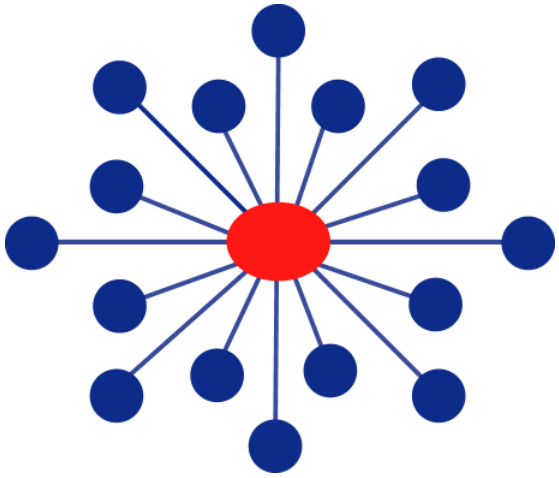

NIDA CTN Protocol 0081

Capturing Opioid Use Disorder Electronically & Patient Reported Outcomes (CODE-PRO)

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Funded by: National Institute on Drug Abuse (NIDA) and the HHS Office of the Assistant Secretary for Planning and Evaluation (ASPE)
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LIST OF ABBREVIATIONS

Abbreviation	Definition
CCTN	Center for the Clinical Trials Network
CDE	Clinical Data Element
CoC	Certificate of Confidentiality
CTN	Clinical Trials Network
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
ED	Emergency Department
EHR	Electronic Health Record
ERC	Ethics Review Committee
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HSP	Human Subject Protection
IRB	Institutional Review Board
IV	Intravenous
LI	Lead Investigator
LN	Lead Node
LTFU	Lost to Follow-up
NIH	National Institutes of Health
NIDA	National Institute on Drug Abuse
OHRP	Office for Human Research Protections
OUD	Opioid Use Disorder
PRO	Patient-reported Outcome
QA	Quality Assurance
RA	Research Associate
SAE	Serious Adverse Event
SRC	Saint Raphael Campus
YNHH	Yale-New Haven Hospital
YSC	York Street Campus

STUDY SYNOPSIS

1.1 Study Objectives

The goal of the project is to enhance capacity to use electronic health record (EHR) data and patient-reported outcomes (PROs) to conduct opioid-related research in Emergency Departments (EDs). Hugo is a cloud-based platform that engages patients as data partners and automates a process that enables patients to easily and securely collect and share health information—including medical records, pharmacy data and survey data such as PROs—directly from a patient's mobile devices or computer. This pilot study will explore the feasibility and usability of Hugo in integrating electronic health records and pharmacy records with patient reported outcomes in ED patients with nonmedical opioid use, opioid use disorder and/or or opioid overdose.

Primary Objective: The primary objective is feasibility testing to determine whether ED patients with opioid use disorder (OUD), non-medical opioid use or opioid overdose will be willing to share electronic health data with researchers and complete PROs delivered by a mobile-based technology platform.

Secondary Objective: The secondary objective is to collect and measure PROs to better understand factors associated with OUD referrals and treatment.

Exploratory Objective: The exploratory objective is to pilot test the integration of PROs into our ED clinical workflow that will be triggered based on PROs collected by surveys.

1.2 Study Design and Outcomes

This is a single-center observational study that will be conducted in the Yale-New Haven Hospital (YNHH) York Street Campus (YSC) and Saint Raphael Campus (SRC) Emergency Departments (ED)s using a convenience sample. It is an exploratory pilot project designed to inform and enhance the use of EHR data and PROs to conduct opioid-related research in the ED.

1.3 Sample Size and Study Population

This study will include approximately 200 ED adult patients with OUD or non-medical opioid use, or those who are being treated for opioid overdose. Given the exploratory nature of this pilot study, the sample size was chosen based on feasibility rather than a formal power analysis.

1.4 Assessment and Duration

The duration of active participation in this study is one month and includes a baseline, one week and 30-day electronic survey. However, researchers will have access to participants' EHR and pharmacy data through Hugo for up to one year after enrollment. The study is estimated to last one year, which includes enrollment and follow-up, data analysis, and manuscript development as outlined below.

3/1/2019 - 4/1/19	Yale IRB Submission/Approval
4/2/19 - 4/12/2019	OHRP Approval
4/15/2019 - 4/30/19	Pilot Enrollment (10 subjects)
5/1/2019 - 10/31/19	Full-time Enrollment (190 subjects)
10/31/19 - 12/31/19	Follow-up Completion (Surveys and EHR extraction)
1/1/20 - 2/28/20	Data Cleaning, Lock, Analysis
3/1/19 - 5/29/20	Manuscript Development

1.5 Safety Reporting

As a minimal risk observational, non-medication and non-intervention study, we will only collect information as reported through the EHR and the PRO and not actively collect adverse event or serious adverse event information. Should any unexpected adverse events occur, they will be reported to the Yale IRB as outlined in the DSMP.

1.6 Analyses

As a pilot feasibility study, we will conduct analyses to assess key outcomes outlined above such as enrollment and survey response rates, in addition to outcomes measured by PROs such as treatment continuation and prescription fulfillment.

INTRODUCTION

1.7 Background and Significance to the Field

In the context of the current opioid overdose crisis, the emergency department (ED) is a key venue to address morbidity and mortality related to substance use disorders. Between 2005 and 2014, the rate of opioid-related ED visits increased 99.4 percent (Weiss, et. al., 2016). Patients with opioid use disorder (OUD) are at risk for high ED utilization. Patients with OUD in an integrated health system were reportedly 7.63 times more likely to have an ED visit compared with controls and 5 times more likely to use ED services (Bahorik, et. al, 2017). It is imperative to examine protocols and processes in emergency medicine settings to address the misuse of pharmaceutical and illicit drugs and improve linkage to treatment.

The field of substance use research should pursue approaches to take advantage of data analytics advances in medicine. The National Drug Abuse Treatment Clinical Trials Network (CTN) is supporting studies designed to build capacity to leverage electronic health records (EHR) for research and to promote “learning healthcare systems” so that practice can inform research and data can inform practice and improve quality of care. There are challenges in using EHR data for research and to optimize patient outcomes in the field. The inclusion of opioid relevant common data elements (CDE)s in clinical data registries and EHRs would improve the quality of research in the field. Researchers in the field need to be able to use outcome data points that are already in the EHR, that is, collected as a part of clinical practice. EHR vendors have been slow to incorporate CDEs related to OUDs and clinical data on OUDs is not being collected in a uniform format. Inconsistencies abound in terminology and the types of information recorded about patients.

Patient-reported outcomes are receiving increasing attention. For example, the HealthMeasures (http://www.healthmeasures.net/) suite of assessments, developed with substantial support from the National Institutes of Health (NIH), is an important resource for assessment and tracking of patient outcomes. The NIH HealthMeasures program consists of four precise, flexible, and comprehensive measurement systems that assess physical, mental, and social health, symptoms, well-being and life satisfaction; along with sensory, motor, and cognitive function.

The NIH PROMIS and NIH Toolkit are included in this group of resources for collecting patient-generated health data. These measures are becoming available in Epic, Cerner, and MyChart EHR systems for point of care use (Jensen, et. al., 2016; PCORI User’s Guide, 2017). Research is demonstrating how PROMIS computer adaptive tests (CATs) can improve patient care such as how preoperative PRO scores predict the likelihood of obtaining a meaningful benefit from surgery (Baumhauer, 2017).

This project will explore the feasibility of collecting patient-reported outcomes electronically. Hugo (http://hugophr.com/) will be used for PRO collection, tracking and data integration. Hugo is a cloud-based platform that engages patients as data partners and automates a process that enables them to easily and securely collect and share health information— including medical records, and survey data such as PROs—directly from a patient's mobile devices. Unlike traditional patient survey tools, Hugo enables linkage with the Epic EHR to support observational studies linking PRO measures to clinical data. In addition to being publicly available for personal use as a way to access personal medical records, Hugo has been used in multiple studies at Yale University and other academic institutions to deliver electronic surveys and collect data from electronic medical records and pharmacies related to a variety of health-related issues, such as heart disease and diabetes.

Hugo Overview, Testing and Acceptability

There are groups that are emerging with the intent to integrate data on behalf of patients and enable those data to be synchronized with the research data but they have yet to establish and validate their data. The Hugo team has several distinguishing features that make their platform preferable over other available systems, such as REDCap DDP, including 1) their track record with industry, academic partners and the FDA and demonstrated ability to integrate data from disparate sources using current APIs and with the capacity to leverage next generation standards; 2) their focus on participant partnership, providing people with agency over their health data; 3) their commitment not to move data without people's permission – the approach ensures that people retain control over how their data are used; 4) their development of Hugo Harmony, an AI approach to improving data quality; 5) their commitment to security and privacy and use of state-of-the art cloud-based approaches; 6) their design which does not require agreements with health systems or other data holder, but rather leverages the rights of individuals to access their data – and builds on rights from HIPAA, HITECH Act and the 21st Century Cures Act; 7) their ability to provide almost real-time data streams, which provide rapid information about outcomes; and 8) their experience in obtaining high response rates using digital devices, with data being encrypted in motion and at rest; 9) their highly regarded user interface; and 10) their method of making it easy to create new surveys without the need for knowledge of a programming language. Of note, REDCap DDP barriers include burdensome setup and ongoing maintenance requiring time and resource investment from the research team and potentially from busy IT resources at research sites.

The Hugo platform has been used across a range of studies to engage populations of varying backgrounds and currently has more than 1,000 users. The age range in prior studies generally ranged from 20 to 80 years, suggesting an acceptability across ages. Hugo is currently in use by several industry, foundation and FDA sponsored studies. With respect to reach, in a study funded by the Aetna Foundation, in partnership with Project Access New Haven, Hugo was used to understand its acceptability to lower health literacy populations. The results showed that this group were avid adopters of the technology, reported being empowered by being given agency over their data, and participated with high response rates (>80%), which were similar for the Spanish version of the platform. Overall, projects using Hugo have typically had ePRO response rates as high as 70% on initial delivery of survey questions. When automated reminders were sent to study participants who did not initially respond, response rates increased further to 80% and above. In some studies response rates through mobile delivery have reached 90% and higher.

Several studies involving Hugo validated the EHR data from Hugo with EHR data collected through traditional methods. As an example, one industry-sponsored project found a 100% match between patient demographic and medical history and event data captured through Hugo and data collected from manual abstraction from the EHR. Importantly, Hugo enabled the capture of events almost immediately after they occurred.

*Note that the statistics referenced above are not currently published in peer-reviewed journals but are private data provided by Hugo, based on their experience and internal evaluation of their platform.

Site Selection:

Yale New Haven Health (YNHH) provides health care to children and adults living in the southern portion of Connecticut, from the New York border to Westerly, Rhode Island. The Yale New Haven Health Emergency Departments at the York Street and Saint Raphael locations provide service to the Greater Bridgeport, New Haven and New London catchment areas. In 2016, 240,000 (19%) individuals within this catchment area received emergency or primary care from YNHHS. Of these, 8,503 unique patients had a diagnosis of alcohol use (AUD) and 1,020 of opioid use disorder (OUD). Forty-three percent of the more than 9,000 SUD patients identified in our EDs were seen two or more times in that year.

Study Rationale:

Given limitations of EHR data related to OUD, this study is designed to inform enhancements to EHR and PROs. We hypothesize that ED patients with OUD, non-medical opioid use, or those who are being treated for opioid overdose will be willing to provide PROs after ED discharge using the electronic platform Hugo, and these PROs can be used to enhance patient care.

OBJECTIVES

1.8 Primary Objective

The primary objective is feasibility testing to determine the proportion of ED patients with OUD, non-medical opioid use or overdose who are willing to share electronic health data with researchers and complete PROs delivered by a mobile-based technology platform. We hypothesize that patients will be willing to enroll and provide PROs both during and after discharge. The primary objective will be measured by the proportion of people who qualify for study criteria and enroll in the study by signing up for Hugo and sharing their EHR with researchers for this study, as well as response rates to electronic surveys and lost-to-follow-up (LTFU) rates among those who enroll. If successful, electronic PROs could offer an opportunity to improve follow-up and treatment among patients with OUD after discharge from the ED.

1.9 Secondary Objectives

The secondary objective is to collect and measure PROs to better understand factors associated with OUD referrals and treatment. Sample outcomes to be measured by surveys include patient experience and ED care, proportion of participants receiving medications for OUD in the ED and referral to treatment by self-report, attendance at follow-up treatment appointment, and post-ED prescription medication pickup.

1.10 Exploratory Objectives

The exploratory objective is to pilot test integration of PRO data into the ED clinical workflow, specifically when PROs identify specific patient barriers that may be addressed by a follow-up call to help patients with the logistics of filling a prescription or scheduling a follow-up appointment. As part of regular ED clinical care at YNHH, we have a follow-up nurse that calls many patients post-ED discharge to facilitate follow-up and clinical care, yet there is no current mechanism for PROs to drive the content or timing of these follow-up calls. For the purposes of this study, the RA will deliver phone calls when participants have trouble filling a prescription or scheduling a

follow-up appointment, as determined by responses in Survey 2. As there is no control group for this study to be used as a comparison, the exploratory objective will simply be described based on our experience throughout the study.

STUDY DESIGN

1.11 Overview of Study Design

Overview:
The Hugo platform will deliver a link to survey in Hugo via email or text message to approximately 200 patients that have been registered as Hugo users by ED and/or research staff and enrolled in the study. Surveys will be delivered to participants at three separate timepoints (baseline, within one week and 30 days following enrollment).

Progression of study design:
As part of the study design, survey timing and content will be changed or updated periodically based on 1-2 month cycles of iterative testing (i.e., up to a total of 4 unique PROs will be delivered throughout the study period) to allow the research team to assess success of specific measures for a particular population and make survey response and patient contact data available to the research team to facilitate patient engagement and action. All questions will be derived from the list of potential PROs included as attachments (Baseline Survey, Survey 2, Survey 3) to this submission and timing of survey distribution may change based on feedback (i.e., 2-day survey may be delivered at 3 or 4 days, if more feasible or appropriate based on PROs delivered). Changes will not compromise the ability to measure outcomes previously described but will be implemented as necessary based on knowledge and experience throughout the study.

A sample timeline for iterative testing includes:

Iteration 1: May 1 – June 30, 2019
Iteration 2: July 1 – Aug 31, 2019
Iteration 3: Sept 1 – Oct 31, 2019
Iteration 4: Nov 1, 2019 – Dec 31, 2019

Sample iterations of PROs include:

Iteration 1:
Baseline survey: Delivered upon enrollment and includes contact information, overdose question, DSM-V criteria for OUD
Survey 2: Delivered 2 days post-enrollment (or 2 days post hospital discharge if the participant was admitted from the ED at enrollment) and includes review of ED care, linkage with treatment and prescriptions post-discharge, and changes in behavior (i.e., TEA assessment)
Survey 3: Delivered 30 days post-enrollment (or 30 days post hospital discharge if the participant was admitted from the ED at enrollment) and includes linkage with treatment and prescriptions, overdose history, and changes in behavior (i.e., TEA assessment)

Iteration 2:
Baseline survey: Same as above
Survey 2: Delivered 3 days post-enrollment (or 3 days post hospital discharge if the participant was admitted from the ED at enrollment) and includes information above, plus or minus certain questions and/or assessments from the list of potential PROs

Survey 3: Delivered 30 days post-enrollment (or 30 days post hospital discharge if the participant was admitted from the ED at enrollment) and includes information above, plus or minus certain questions and/or assessments from the list of potential PROs

Study Flow:

1. Upon enrollment, participants will be prompted to complete a baseline survey delivered via Hugo during their ED visit.

2. Participants will receive a follow-up survey via Hugo via email or text within one week of enrollment (or within one week of post hospital discharge if the participant was admitted from the ED at enrollment). If patients identify difficulties with obtaining a follow-up appointment or picking up medications, to test the ability to integrate PROs into our clinical workflow, patients may receive a follow-up call to assist with the logistics of obtaining a follow-up appointment or picking up medications. During this call, the RA will clarify issues related to medication pick-up or accessing treatment services if they are identified in the survey and will refer patient to follow-up nurse as needed. This call is not to provide counseling or treatment, or intended to provide an intervention.

3. Participants will receive a final survey within one month of enrollment.

4. If at any point participants fail to complete a survey, they will receive up to three email or text reminders and one phone call from the study RA to encourage survey completion. If no participant contact is elicited, the study RA will call the secondary contact person in an effort to locate the participant. Participants who fail to complete surveys within one month of initial follow-up survey receipt will be considered lost to follow-up.

Data Management:
A summary of survey data will be available 24/7 to researchers via the secure Hugo research dashboard. This data is updated in real-time and will be monitored weekly by a study RA to track survey completion, reminders and participants that are LTFU. Individual survey responses will be managed by Hugo and shared with study staff via secure file transfer every two weeks or as needed for analysis and development.

In addition, Hugo will automatically pull select data fields from each participant's shared records (EHR and pharmacy data) on a weekly basis. The infrastructure and agreements for secure data sharing between EHRs and pharmacies with Hugo are already established and occur automatically once patients link their accounts. Researchers will have access to data fields via Hugo for one year after enrollment for each participant and Hugo will send data fields to Yale via secure file transfer every two weeks or as needed. Access to data fields is permitted for one year to ensure that researchers have access to all participants data from the start of enrollment through analysis completion, should it be needed. Therefore, patients consent to sharing data for one year, although those enrolled later in the study will not be sharing data for the entire year.
Survey, EHR and pharmacy data will be used to assess the study outcomes outlined above.

1.12 Duration of Study Schedule

Each subject will be actively on study until surveys are completed or until end of study eligibility period. Their passive participation in data sharing will last one year following enrollment.

OUTCOME MEASURES

1.13 Primary Outcome Measures

The primary outcome measures are the proportion of people who qualify for study criteria and enroll in the study, as well as response and follow-up rates among those who enroll.

1.14 Secondary Outcome Measures

PRO measures, such as patient experience, TEA assessment, and the proportion of participants receiving OUD medication and referral in the ED, enrolling in treatment and refilling prescriptions following their visit.

1.15 Other Outcome Measures

Proportion of patients who identify insurance, transportation barriers to filling follow-up prescription medications from the ED, and proportion of participants successful overcoming barriers after phone call.

1.16 Study Timeline

After receiving funder approval of the final protocol, Institutional Review Board (IRB) approval will then be obtained from the Yale University IRB. Once approved, enrollment will take place in the following year until up to 200 patients are enrolled or if the study enrollment time period ends per funding and program duration. Enrollment will be rolled out slowly, with an initial pilot period of up to one month. During this time, up to ten patients will be enrolled to ensure proper functionality of the Hugo tool, PRO delivery, EHR integration and data transfer. Their data will be included in the final data analysis.

Once all surveys and follow-up are complete for the study, EHR data collection will be finalized within two months of the final participant enrollment. Therefore, data lock is projected to occur approximately 12 months after IRB approval.

STUDY POPULATION

The study population consists of adult ED patients with OUD or non-medical opioid use, or those who are being treated for opioid overdose.

1.17 Participant Inclusion Criteria

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study:

- Adult patient presenting to the YNHH YSC or SRC EDs
- History of opioid use disorder or non-medical use of opioids, as measured by screening assessment OR receiving treatment for opioid overdose
- Willingness and ability to complete electronic surveys via a smartphone or computer

1.18 Participant Exclusion Criteria

Individuals meeting any of the following exclusion criteria at baseline will be excluded from study:

- <18 years of age
- Inability to communicate in English
- Inability to provide consent (for example, due to psychosis, intoxication, severe mental illness, lack of capacity per clinician evaluation, or other reason)
- Awaiting emergent psychiatric evaluation

1.19 Strategies for Recruitment and Retention

Identification:
Participants will be identified in multiple ways, including:

- Electronic trackboard: The RA will continually monitor the ED trackboard for patients with a chief complaint of overdose or intoxication and conduct a brief EHR review for patients with these relevant chief complaints to assess inclusion/exclusion criteria. For patients that appear eligible, the RA will ask the treating ED clinician if the patient is currently clinically sober and meets inclusion and exclusion criteria to the best of the ED clinician's knowledge. The RA will then approach any patients that remain eligible. If a patient appears eligible but is currently intoxicated, he or she will be approached once the clinician deems them sober enough to have the capacity to consent to research.
- Referrals: All ED staff will be informed of our study and asked to refer patients when appropriate. Staff includes physicians, nurses, technicians and Project ASSERT staff. Project ASSERT is a YNHH ED service provided by health promotion advocates that connects patients with substance use disorders to treatment. ED staff will alert the RA of potential patients in person, by phone, email or Epic inbox.

Special Cases: It is possible that eligible patients screened in the ED may be admitted, in which case they will be followed to the inpatient floor if necessary to complete enrollment. Patients who are approached by research staff to participate, but decline participation, will not be re-approached during hospitalization, even if they were clinically intoxicated at the time they declined participation. It is also possible that participants enrolled in the ED could be on parole, which by definition qualifies as a prisoner in the state of Connecticut. For this reason, we will obtain OHRP Prisoner Certification to include individuals defined as prisoners by the state or federal regulations, which will be obtained prior to beginning enrollment. We do not plan to follow participants if incarcerated, however, as surveys are electronic and it is highly unlikely that prisoners would have access to a smartphone or computer while incarcerated. We will also not ask any questions at baseline or follow-up regarding parole or incarceration, given OHRP approval to include such participants.

Retention:
Participants will be compensated for the time to complete surveys, which should offset participant time as a barrier to follow-up survey completion. Participants who do not complete surveys within 24 hours of receipt will receive up to three email or text reminders (depending on their account preferences) and one reminder phone call as an attempt to obtain survey completion. Participants who fail to complete surveys within one month of initial receipt will be considered lost to follow-up.

SITE SELECTION

This is a single-site study conducted at the YNHH YSC and SRC EDs. The site was selected as it is the recipient of the study grant and capable of meeting all requirements related to patient population, staff, and resources.

STUDY PROCEDURES

1.20 Screening

1.20.1 Screening Assessment

In combination with evaluation of eligibility criteria mentioned above, eligibility of OUD or non-medical use of opioids will be determined using the screening assessment outlined below. During the screening assessment, visitors and family will be asked to leave the room and the remainder of the consent process and interview will occur without visitors except for when the patient specifically requests that their visitor be allowed to stay. The screening assessment will not be required for patients who are being treated for OUD overdose. To avoid interrupting patient care, the logistics of conducting screening in a medical setting require that the screening process be relatively brief. During defined recruitment hours, research staff assigned to the study will screen ED patients who are possibly eligible for the study. Depending on the patient flow, patients will be approached either prior to or after the evaluation by a clinician.

Research staff will approach patients consecutively and ask them if they are willing to participate in anonymous screening for participation in a health study. Participants will provide verbal (not signed) consent for the anonymous collection of screening data, using a brief IRB-approved script. For each day of screening, the number of patient refusals and other reasons for patient inability to participate will be recorded on the Screening Log to determine whether they met inclusion criteria (and if not, why). The RA will document the screening and eligibility status of all individuals approached on the Screening Log. Screening efforts will continue until recruitment hours have ended.

All participants reporting any opioid use during screening will receive a brochure on overdose prevention and a Project ASSERT brochure, which includes information on local treatment resources and contact information of hospital staff that specialize in referrals to treatment.

1.20.2 Informed Written Consent Procedures for Participants

Consent will be obtained bedside in the ED. Potential study subjects will be approached by the RA and offered participation in the study. Inclusion and exclusion criteria will be reviewed by the research assistant and if the patient is agreeable to study participation, the informed consent document will be reviewed with the patient. Study procedures and the potential risks and benefits of participating in the trial will be explained. Staff will be available to answer questions about the consent form while participants are reviewing it.

Candidates will be informed that their medical care will not be adversely affected if they decline to participate in this study. The candidate will be informed that their participation is voluntary, and they may withdraw from the study at any time, for any reason, and without penalty. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice.

1.21 HIPAA Authorization and Medical Record Release Forms

Authorization from participants for use of protected health information is included in the informed consent form and is in compliance with Yale IRB policies. As noted in this protocol, Hugo is not subject to HIPAA and by agreeing to set up an account and link data with our research study, participants are agreeing to release their EHR and/or pharmacy data with Hugo and researchers.

1.22 Baseline Visit

Using strategies outlined above for identification and screening, the RA will collect informed consent from willing participants that meet all eligibility criteria. After providing informed consent, the following steps will occur:

1. Using the participant's own mobile device or a device belonging to the research team, the RA will assist the participant with creating an account with Hugo, if they don't have one already. This process will require participants to enter basic information including first name, last name, email address, and to choose a secure password. They will also be prompted to accept standard terms and conditions and a privacy notice from Hugo. The participant will then check their email and click the confirmation link to activate their new account. If participants do not have an email account and wish to create one, a member of the research team will help them set one up from variety of free and commercial email providers, such as Gmail and Yahoo.

2. Once a participant's Hugo account is activated, they will be prompted to link their patient portals by presenting a list of participating health systems and pharmacies. They can select the systems where they have received care and enter their patient portal username and password as required (all of these are password-protected). If participants forget their password, they can request a link to reset it be sent to their email of record. If necessary, the research assistant will assist participants in setting up a new YNHH MyChart account, obtaining a YNHH MyChart username, and help resetting their YNHH MyChart password.

3. The RA will help the patient link their Hugo account with this research study and help answer any questions related to data sharing. Once linked, the participant will immediately receive a secure link to their baseline questionnaire, which will be sent by email and/or text depending on the preferences chosen during account set up. Participants will be asked to complete this survey prior to discharge and the RA will be available to assist with any technical or study-related questions.

1.23 Follow-up

After enrollment and completion of the baseline survey, follow-up includes two additional electronic questionnaires outlined in the study design. Questionnaires will be sent within one week of enrollment and at 30-days. If patients are admitted to the hospital from the ED at enrollment, their follow-up questionnaires will be sent within one week of hospital discharge and at 30-days post hospital discharge. Data from participants EHRs and pharmacies will also be extracted by Hugo and shared with Yale in the timetable mentioned above.

1.24 Premature Withdrawal of Participants

All participants will be asked to complete all three surveys in the first month and agree to sharing EHR and pharmacy data for one year from enrollment. Participation will continue unless they withdraw consent, die, or the investigator or funder decides to discontinue their enrollment for any reason. Reasons for the investigator or funder terminating a participant from the study may include, but are not limited to, the participant becoming a threat to self or others, lack of funding, or early termination of the study for safety or effectiveness reasons. For participants who voluntarily withdraw, no new health information will be gathered after the date of withdrawal. However, information that has already been collected will still be used and given to others until the end of the research study to insure the integrity of the study and/or study oversight. Patients who withdraw consent will not be allowed to enroll in the study at a later time.

1.25 Study Halting Rules

As a low-risk observational study, safety issues are unlikely. However, the study will be stopped early should any ethical issues or breaches to data security, patient confidentiality or IRB policies occur. Should the study be prematurely terminated or temporarily suspended, the LI will promptly inform the IRB and funder and provide the reason(s) for the termination or temporary suspension. If all issues are addressed, it is possible that the study can resume pending approval from the IRB and funder.

1.26 Participant Reimbursement

Participants will receive up to $30 for participation in this study. Payments will be made in the form of gift cards and include a $10 payment after completion of enrollment, and each additional survey. Gift cards will be emailed to participants upon completion of each survey.

STUDY ASSESSMENTS

Study assessments are outlined below.

1. Quick Screen Form: To be used during baseline in-person interview prior to enrollment with any potentially eligible patient who is being screened for OUD or non-medical opioid use. It includes inclusion/exclusion criteria, brief questions about substance use and past 30-day opioid use, and a question about access to a smartphone or computer.

2. Baseline Survey: To be completed by participants electronically during their baseline visit after consenting, creating their Hugo account and sharing data with our study. Note that content of the baseline survey may change based on the iterations of the PROs outlined in this protocol and all questions will be derived from the list of potential PROs included with this protocol. It may include demographics, DSM-V criteria for OUD, and/or overdose history.

3. Survey 2: To be completed by participants electronically within one week of enrollment, or one week after hospital discharge if the participant is admitted from the ED at enrollment. Note that timing and content of survey 2 may change based on the iterations of the PROs outlined in this protocol and all questions will be derived from the list of potential PROs included with this protocol. It may include questions about patient experience during their initial ED visit, subsequent connection with treatment and prescriptions, overdose history, recent drug use, and overall health.

4. Survey 3: To be completed by participants electronically 30 days following enrollment, or 30 days after hospital discharge if the participant is admitted from the ED at enrollment. Note that content of survey 3 may change based on the iterations of the PROs outlined in the protocol and all questions will be derived from the list of PROs included with this protocol. It may include questions about connection with treatment and prescriptions, overdose history, recent drug use, and overall health.

5. EHR Data Extraction: In addition to survey data, the following fields will be automatically extracted from participants EHRs: Name, Age, Gender, Date of birth, Medical record number, Vital signs, Provider encounters, Family history, Laboratory findings, Procedures, Problem list, ICD diagnoses, Medicines administered and prescribed. These fields will be used for secondary and/or future exploratory analyses as they relate to PROs and can be extracted as far back as each participant's available EHR.

6. Pharmacy Data Extraction: Prescription refill data will be automatically extracted from participating pharmacies that currently share data with Hugo, such as CVS and Walgreens, and are linked to each participant's Hugo account. Available prescription data will be used for secondary and/or future exploratory analyses as it relates to PROs.

7. Case Report Form – Enrollment: Used to document whether participants required assistance setting up a MyChart or pharmacy account to be linked with Hugo.

8. Case Report Form – Follow-up Call: Used to document information collected during follow-up calls, when applicable.

TRAINING REQUIREMENTS

All study personnel such as LI, co-lead investigators, study RA, project managers and data analysts will be listed on the Yale IRB submission. Per Yale IRB policies, all staff must have completed HIPAA training, Human Subjects Protection Training, Good Clinical Practice Training and a conflict of interest form (investigators only) for the submission to be approved. In addition to these trainings, the LI will provide protocol specific training and ensure that all staff understand the study protocol and follow all guidelines outlined in this document.

STATISTICAL DESIGN AND ANALYSES

As an observational feasibility pilot study, statistical design and analysis will be largely exploratory and directed by outcomes outlined above. Baseline demographic and clinical variables will be summarized for participants enrolled and 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. When appropriate, outcomes will be evaluated using a two-sided test with a type I error rate of 5%. Statistical analysis will be performed using R statistical software. The primary outcome will be measured by the proportion of people who qualify for study criteria and enroll in the study, as well as response and LTFU rates among those who enroll. Secondary outcomes will include PRO measures, which may include patient attitudes and experience, proportion of participants receiving OUD medication and MAT referral in the ED, enrolling in treatment and refilling prescriptions following their visit. When possible, changes in PROs over the course of the study will also be analyzed as appropriate. While adverse events are not anticipated, any adverse events that do occur will be described in the analysis as appropriate.

REGULATORY COMPLIANCE, REPORTING AND MONITORING

1.27 Regulatory 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 Regulations for the Protection of Human Subjects codified in the International Council for Harmonization Good Clinical Practice (GCP) Guidelines, and all other applicable regulatory requirements.

1.28 Statement of Compliance

This trial will be conducted in compliance with the appropriate protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Yale will obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from the Yale IRB. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by the Yale IRB and any amendments to the protocol or consent materials will be approved before they are implemented. Unanticipated problems involving risk to study participants will be promptly reported to and reviewed by Yale IRB, according to its usual procedures.

1.29 Institutional Review Board Approval

Prior to initiating the study, the lead investigator will obtain written IRB approval to conduct the study at YNHH. If changes to the study protocol become necessary, protocol amendments will be submitted in writing by the investigators for IRB approval prior to implementation. In addition, IRBs

will approve all consent forms, recruitment materials, and any materials given to the participant, and any changes made to these documents throughout study implementation. For changes to the consent form, a decision will be made regarding whether previously consented participants need to be re-consented. IRB continuing review will be performed annually, or at a greater frequency contingent upon the complexity and risk of the study. The LI 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. The LI is responsible for providing copies to NIH of all current IRB approval notices, IRB-approved consent documents, and approval for all protocol modifications.

1.30 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 and will be written for the purposes of this study. The informed consent form will include all the required elements of informed consent and may contain additional relevant consent elements and NIDA CCTN specific additional elements. 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(a), as well as pertinent additional elements detailed in 21 CFR 50.25(b) and 45 CFR 46.116(b), a copy of the consent will be reviewed by Emmes and CCTN Scientific Officers prior to obtaining approval from the Yale IRB. 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 original signed informed consent for every participant in a locked, secure location that is in compliance with all applicable IRB and institutional policies and that would be accessible to the Lead Investigator and others as required. Every study participant should be given a copy of the signed consent form.

Prior to informed consent, research staff will explain the study to the potential participant and provide a copy of the consent to read. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and their rights as research participants. Extensive discussion of risks and possible benefits will be provided to the participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to 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 staff member will review each section of the IRB-approved informed consent form in detail and answer any questions the participant may pose. The participant, or participant's legally authorized representative, will consent by signing and dating the consent document. The person obtaining consent and a witness, if required by the local IRB(s), will also sign and date the consent document. Staff members will be delegated by the LI to obtain informed consent approved by the IRB and 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 the protocol is amended in a way that may affect participants' participation in the trial. A copy of the informed consent will be given to a prospective participant to review during the consent process and to keep for reference. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The participant will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason without penalty. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice. The study site will be responsible for

maintaining signed consent forms as source documents for quality assurance review and regulatory compliance.

1.31 Quality Assurance Monitoring

In accordance with federal regulations, the study funder is responsible for ensuring proper monitoring of an investigation and ensuring that the investigation is conducted in accordance with the protocol. The Lead Investigator and CTN Node staff 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 can be reported as a protocol deviation and submitted to the study funder and study IRB for further review.

1.32 Participant and Data Confidentiality

Confidentiality will be maintained in accordance with all applicable federal regulations and/or state/Commonwealth law and regulations. The investigator affirms that all study information 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.

To further protect the privacy of study participants, the NIH automatically provides a federal Certificate of Confidentiality (CoC) for this study, which protects identifiable research information from forced disclosure. This protects participants against disclosure of sensitive information (e.g., drug use). The CoC allows the investigator and others who have access to research records to permanently refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level, excepting certain circumstances.

By protecting researchers and institutions from being compelled to disclose information that would identify research participants, the Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants. The NIH office that issues the CoC will be advised of changes in the CoC application information. The participating site will be notified if CoC revision is necessary. Participant records will be held confidential by the use of study codes for identifying participants, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

<u>Data Sharing Between Yale and Hugo</u>
While Hugo is not subject to HIPAA, as outlined elsewhere in this protocol, data sharing between the two sites adheres to industry standards and protects patient confidentiality. Hugo obtains data on behalf of the participant, who grants permission for the data, as it accumulates, to be sent to the study. The design is to enable the participant to keep their information and share it with the study. The institutions that are Meaningful Use Stage 2 compliant (which includes almost all health centers in the US) are mandated to provide people their data – and the 21st Century Cures Act reinforces that a platform such as Hugo is a suitable means to help people get their data. There is no need for an agreement with the health system and the Yale IRB has reviewed and approved this approach. Hugo has no obligation to the healthcare facility – though it could provide the information into the EHR if the health system allowed for it to flow that way. Hugo's obligations are to the participant – and keeps the data on behalf of the participant. In this study, the primary focus of Hugo is to obtain survey information from the patient – and in this case the individual will retain their responses and have then sent to the study. Once the data are in the research

database, the oversight of the research, per usual protocols, will be enforced. Hugo is committed not to move, send or share a person's data without their explicit permission.

1.32.1 Health Information Portability Accountability Act (HIPAA)

The site will be responsible for communicating with the IRB of record and obtaining the appropriate approvals or waivers to be in regulatory compliance. Releases of participant identifying information that are permitted by the HIPAA regulations, but which are prohibited by other applicable federal regulations and/or state/Commonwealth law and regulation, are prohibited.

1.33 Investigator Assurances

The site must file (or have previously filed) a Federal Wide Assurance (FWA) with the Department of Health and Human Services Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects, with documentation sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103(b) and (f)). Prior to initiating the study, the Principal Investigator at the study site will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

1.33.1 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. All investigators will confirm to the funder annually that they have met their institutional financial disclosure requirements via a Financial Disclosure Tracking Form available on the CTN website.

1.34 Clinical Monitoring

The Lead Investigator, Co-Investigators, and/or CTN Node staff will examine whether study procedures are conducted appropriately and that study data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulations. They will audit, at mutually agreed upon times, regulatory documents, informed consent forms and corresponding source documents for each participant. These staff members will have the opportunity and ability to review any study-associated document or file.

Designated Lead or Co-Investigators and/or CTN Node staff will assess whether submitted data are accurate and in agreement with source documentation and will also review regulatory/essential documents such as correspondence with the IRB. Areas of particular concern will be participant informed consent forms, protocol adherence, reported safety events and corresponding assessments, and Principal Investigator oversight and involvement in the trial.

Qualified node personnel (Node Quality Assurance monitors) or other designated party(ies) such as study Research Coordinator will provide site management during the study. Node QA staff or other designated party(ies) will audit source documentation, including informed consent forms and HIPAA forms. This will take place as specified by the LI and will occur as often as needed to help prevent, detect, and correct problems at the study site.

1.35 Inclusion of Women and Minorities

The study site should aim and take steps to enroll a diverse study population. If difficulty is encountered in recruiting an adequate number of women and/or minorities, the difficulties involved in recruitment will be discussed with study staff.

1.36 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all-important communications. Regulatory files will be checked by the LI for regulatory document compliance prior to study initiation, throughout the study, as well as at study closure. Upon study end, the LI will ensure that all documentation complies with regulatory requirements and that analysis of identifiable information has been completed prior to submitting to the Yale IRB for study closure.

1.37 Records Retention and Requirements

Research records for all study participants (e.g., case report forms, source documents, signed consent form, 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. While the Hugo platform will have real-time access to participant-shared data for up to one-year from enrollment, the data downloaded for the purposes of this study is considered a research record and will be maintained for the same duration as other study materials. These records are also to be maintained in compliance with IRB, state and federal requirements, whichever is longest. The funder must be notified in writing and acknowledgment must be received by the site prior to the destruction or relocation of research records.

1.38 Reporting to Funder

The Lead investigator agrees to submit accurate, complete, legible and timely reports to the funder, as required. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the study or increase risk to study participants. Given the short duration of the study, safety reporting will occur as needed (if applicable, as described elsewhere in this protocol) and at the end of the study. At the completion of the trial, the Lead Investigator will provide a final report to the funder.

1.39 Audits

The Funder has an obligation to ensure that this trial is conducted according to good research practice guidelines and may perform quality assurance audits for protocol compliance. The Lead Investigator and authorized staff from the New England Consortium Node; the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN, the study funder); 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.

1.40 Study Documentation

The site will maintain appropriate study documentation (including medical and research records) for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. Study documentation includes all completed assessments, surveys, approved 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-funded study, each site will permit authorized representatives from NIDA and regulatory agencies to examine (and when permitted by law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the

study safety, progress, and data validity.

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

1.41 Protocol Deviations

Any departure from procedures and requirements outlined in the protocol will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. 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 NIDA or NIDA designee, with overall approval by the IRB of record. 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.

1.42 Safety Monitoring

1.42.1 Data and Safety Monitoring Board (DSMB)

As a minimal-risk study, the study does not require an independent NIDA CTN DSMB. However, a detailed Data and Safety Monitoring Plan (DSMP) is included as an appendix, which incorporates requirements of both the Yale IRB and NIDA CTN.

1.42.2 Adverse Events (AEs)

As a minimal risk observational, non-medication intervention study, we will only collect information as reported through the EHR and the PRO and not specifically collect adverse event or serious adverse event information. The Lead Investigator will be responsible for the management of information gathered by the RAs and develop processes and procedures at the site for that management. The LI will designate a backup in the event she will not be available. The appropriate response and action will be determined in collaboration with the LI, Yale IRB and funder and carried out by the appropriate party.

DATA MANAGEMENT

1.43 Site Responsibilities

Data oversight will be conducted by study team members at Yale School of Medicine in collaboration with Hugo. Hugo is responsible for maintaining and securely transferring all electronic data captured through their tool, which includes survey responses, EHR data and pharmacy data, outlined in this protocol. Yale is responsible for conducting ongoing data monitoring activities and performing data cleaning and all data analysis.

1.44 Data Collection and Security

Hugo:
Participants will be requested to submit data from their personal health records to the study over SSL with a minimum of 128-bit encryption. This data will be downloaded to a secure server with Yale with access available only to study personnel for one year following enrollment. Data will be received from the Hugo platform at scheduled intervals via secure webservice endpoint and stored on a password-protected encrypted university computer or secure university server and stored for the duration of the study. The Hugo platform has undergone a thorough security analysis by Yale University to ensure its safety and confidentiality and details regarding their data management are included in the attached Hugo Security Statement and Privacy Notice.

Yale:
Paper files, such as signed consent forms, will be in locked files in the Emergency Department's research room. All study data will be stored on secure university-maintained computers and servers, with restricted access to investigators and staff listed on this protocol. All data will be transferred over encrypted connections and stored on Yale or YNHH-managed hardware that is suitable for PHI. Data will also be transferred with Yale-managed IronKey encrypted portable devices. Only study personnel directly involved in data analysis with a need to access PHI will have access to these data. After the completion of study enrollment, all data will be de-identified for ongoing analysis and patients will only be identified by study ID. However, study records will be maintained for three years per IRB guidelines, after which paper documents will be destroyed. Following the data lock, electronic data will be de-identified and shared the NIDA Data Share website, as outlined in this protocol.

When research assistants travel between YSC and SRC, they will utilize the YNHHS interfacility shuttle and will keep all study devices (i.e., laptop and tablet), signed consent forms, and any other documentation with PHI on their person, or locked in the YSC or SRC research rooms at all times.

PUBLICATIONS AND OTHER RIGHTS

Per NIH policy, the results of the proposed trial are to be made available to the research community and to the public at large. The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN.

PROTOCOL SIGNATURE PAGE

FUNDER'S REPRESENTATIVE (CCTN SCIENTIFIC OFFICER OR DESIGNEE)

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version X of the protocol and agree to conduct this clinical study in accordance with the design and provisions specified therein.
- I agree to follow the protocol as written except in cases where necessary to protect the safety, rights, or welfare of a participant, an alteration is required, and the funder 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 _____

APPENDIX B: DATA AND SAFETY MONITORING PLAN

1.0 BRIEF STUDY OVERVIEW

The goal of this project is to enhance capacity to use EHR data and PROs to conduct opioid-related research in EDs. For this project, Hugo will be used to explore the feasibility and usability of electronic PRO measurement through patient portals.

2.0 OVERSIGHT OF CLINICAL RESPONSIBILITIES

A. Lead Investigator

The Lead Investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews. During the review process the Lead Investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The LI will monitor the protocol for integrity and operations through several means. First, the LI will directly observe initial patient enrollments by trained research assistants. In addition, case-by-case feedback regarding enrollment and participation will be conducted for the first 10 enrollments to ensure no protocol violations or unexpected issues. Given the short-period of this study, the LI will also be available by phone during all enrollment times to provide additional support and resources for any challenges encountered during the study period.

The LI, the Institutional Review Board (IRB) and funder (National Institutes of Health) have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Lead Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators, study personnel and funders of all UPIRSOs and adverse events that occur during the conduct of this research project via regular study meetings or email, as appropriate, within 5 days becoming known to the Lead Investigator.

B. Management of Risks to Participants

Confidentiality

Confidentiality of participant records will be secured using study codes for identifying participants, and secure storage of any documents that have participant identifiers on site, as well as secure computing procedures for entering and transferring electronic data. The documents or logs linking the study codes with the study participant on site will be kept locked separately from the study files and the medical records. 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

The RA will be adequately trained by the LI to ensure that all participants are eligible and safe to enter the study. When necessary, the RA will obtain guidance from ED providers and/or LI when in need of any guidance on inclusion/exclusion criteria and/or safety concerns.

Pregnancy

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

Study Specific Risks

The risks associated with this study are minimal and include loss of privacy or confidentiality, potential increased length of stay in the Emergency Department, and potential inconvenience and discomfort answering surveys, which include questions about drug use. The risk to patient privacy is no different with this study than it is with any other study that securely collects and appropriately stores personally identifiable information or protected health information. Indeed, the risk may be less since researchers are only getting access to patient data from the time of enrollment forward for 1 year; there is no open access to the patient's entire medical record. The Hugo S4S platform, like many other personal health records, is not a covered entity; therefore, the HIPAA privacy rule does not apply to this platform. The Hugo platform does take all necessary precautions, including industry-standard encryption of data in transit and at rest, to minimize privacy and security risks to personally identifiable information and PHI stored on behalf of study participants.

To address the risks above, patient privacy and confidentiality will be respected at all times and a private area will be arranged for patient screening, enrollment and interviews when feasible. Study enrollment should not delay discharge from the Emergency Department, and if the patient is otherwise ready for discharge upon study enrollment, they will be given the option to not participate. In respect to minimizing risks for data exposure, all patient data will be collected, handled, and stored according the most rigorous accepted standards. Staff involved in the study will be appropriately trained to maximize data security and technical systems will meet or exceed requirements imposed by HIPAA. Sensitive information will always be encrypted in transit and at rest. Paper files will be in locked files in the Emergency Department's research room.

3.0 DATA MANAGEMENT PROCEDURES AND RESPONSIBLITIES

With oversight from the LI, the Yale study team (study investigators and project manager) will oversee all data management and analysis for this protocol, in collaboration with Hugo. Together, they will be responsible for the integrity and confidentiality of data management and analysis.

Hugo is responsible for maintaining and securely transferring all electronic data captured through their tool, which includes survey responses, EHR data and pharmacy data, outlined in this protocol. Yale is responsible for maintaining accurate, complete and up-to-date research records, conducting ongoing data monitoring activities, performing data cleaning activities prior to the final study database lock and performing data analysis.

4.0 DATABASE LOCK AND TRANSFER

At the conclusion of data collection for the study, Yale will perform final data cleaning activities and will "lock" the study database from further modification. De-identified versions of these datasets will also be provided to the NIDA CCTN-designated parties for posting on the NIDA Data Share website, as well as storage and archiving.

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

APPENDIX C: REFERENCES

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CDC. Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics; 2016. Available at http://wonder.cdc.gov

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https://www.drugabuse.gov/about-nida/organization/cctn/ctn/resources/common-data-elements-cde

NIDA CDE Module: SUD Treatment/Status:
https://cde.drugabuse.gov/instrument/c0de142b- 4a82-99a1-e040-bb89ad434140/module/c0de142b-4b57-99a1-e040-bb89ad434140

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