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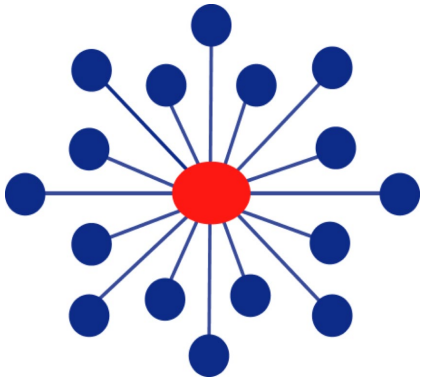

NIDA CTN-0079-A1

Emergency Department Outcomes for Patients with Opioid Use Disorder

(Project ACT)

Funded by: National Institute on Drug Abuse (NIDA)

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACEP	American College of Emergency Physicians
AE	Adverse Event
ASAM	American Society of Addiction Medicine
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
BRANY	Biomedical Research Alliance of New York
BUP	Buprenorphine
BUP-NX	Buprenorphine+Naloxone (Suboxone®)
CCC	Clinical Coordinating Center
CCTN	Center for Clinical Trials Network
CFR	Code of Federal Regulations
CMS	Centers for Medicare and Medicaid Services
CoC	Certificate of Confidentiality
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Form
CQI	Continuous Quality Improvement
CTN	Clinical Trials Network
DEA	Drug Enforcement Agency
DHHS	Department of Health and Human Services
DM	Data Management
DSC	Data and Statistics Center
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
ED	Emergency Department
EDC	Electronic Data Capture
EMR	Electronic Medical Record
EMS	Emergency Medical Service
ERC	Ethics Review Committee
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HSP	Human Subject Protection
ICD	International Classification of Diseases
IF	Implementation Facilitation
IRB	Institutional Review Board
LI	Lead Investigator
LN	Lead Node
MD	Medical Doctor

Abbreviation	Definition
MDMA	Methylenedioxymethamphetamine (Ecstasy)
ME	Medical Examiner
mg	Milligrams
MOP	Manual of Operations
MOUD	Medication for Opioid Use Disorder
NA	Narcotic Anonymous
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NP	Nurse Practitioner
NQF	National Quality Forum
NYU HEAL	New York University Health Evaluation & Analytics Lab
OHRP	Office for Human Research Protections
ORCA	Organizational Readiness to Change Assessment
OTP	Opioid Treatment Program
OUD	Opioid Use Disorder
PA	Physician Assistant
PARiHS	Promoting Action on Research Implementation in Health Services
PCP	Phencyclidine
PDMP	Prescription Drug Monitoring Program
PHI	Protected Health Information
PI	Principal Investigator
PII	Personally Identifiable Information (PII)
PROMIS-29	Patient-Reported Outcomes Measurement Information System (PROMIS)
QA	Quality Assurance
RE-AIM	Reach, Effectiveness, Adoption, Implementation, Maintenance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIRT	Screening, Brief Intervention, Referral for Treatment
SL-BUP	Sublingual buprenorphine
THC	Tetrahydrocannabinol
TLFB	Timeline Follow-Back
UDS	Urine Drug Screen
XR-BUP	Injectable extended-release buprenorphine
X-Waiver	Drug Enforcement Agency DATA 2000 certification necessary to prescribe BUP

2.0 STUDY SYNOPSIS

2.1 Clarification of Terminology

See below for a list of terminology used throughout this protocol, which are described and defined in more detail in section 8.0 and elsewhere in the protocol:

- Emergency Department (ED)-initiated Buprenorphine (BUP) clinical program refers to all the components of clinical care required to initiate treatment with BUP to ED patients with opioid use disorder (OUD) and provide them with access to ongoing treatment through referral. Site-specific clinical protocols were introduced in and by each clinical site/ED during the parent CTN-0079 study aided by study-sponsored subject matter expertise and other Implementation Facilitation (IF) activities. Each site-specific clinical protocol provides clinical guidance related to assessing a patient's "eligibility and willingness" to receive ED-initiated BUP (screening/identification followed by further assessments) and the other critical actions to treatment initiation and referral.
- ED-initiated BUP refers to BUP administered and/or prescribed to an ED patient as part of the ED visit. Referral to ongoing treatment should be provided to all patients receiving BUP treatment initiation.
- ED-expedited BUP refers to a patient being transferred directly or provided with specific "warm hand off" of care to a treatment setting or provider capable of prescribing or administering BUP within 24 hours of ED discharge. This includes direct transport or handoff to outpatient provider immediately from the ED, an appointment in clinic within 24 hours, or transfer to inpatient treatment. This indirect BUP treatment initiation is a means of providing expedited access to treatment for patients who are candidates for ED-initiated BUP but who are not in sufficient withdrawal to administer BUP and/or when there may or may not be a provider who has the DEA DATA 2000 "X-wavier" licensure required to prescribe BUP.
- ED-initiated/expedited BUP (abbreviation for "ED-initiated BUP and/or ED-expedited BUP") refers to a composite measure of either ED-initiated BUP and/or ED-expedited BUP occurring.
- Candidate for ED-initiated BUP refers to an individual who is documented or presumed (based on available data) to be clinically appropriate to be started on BUP treatment for OUD during the ED visit via either ED-initiated BUP or ED-expedited BUP. This terminology will be used in place of the term "eligible and willing to receive ED-initiated BUP" that was used in the parent CTN-0079 study. Although the terms are essentially synonymous, this change will help distinguish patients who meet inclusion criteria for the clinical intervention (ED-initiated/ expedited BUP) from those who meet the additional criteria for research participation. In addition to changing the terminology/nomenclature, we have amended the operational definition and methods of determining candidacy for ED-initiated BUP for this study by incorporating lessons learned from the parent study. The clinical documentation requirements to meet criteria of "candidate" are less stringent than was required in the parent study to be "eligible and willing" and are further described in section 8.1. In other words, all patients who would have met the CTN-0079 parent study criteria of "eligible and willing to receive ED-initiated BUP" will also meet criteria to be a "candidate for ED-initiated BUP." Also of note, any patient who meets the criteria to be a candidate for ED-initiated BUP is also a candidate for ED-expedited BUP.

2.2 Study Synopsis

CTN-0079-A1 will evaluate the extent of diffusion and the sustainability of the Emergency Department (ED)-initiated buprenorphine (BUP) clinical programs (inclusive of opioid use disorder [OUD] screening, BUP treatment initiation, and referral for treatment) introduced at each of the three clinical sites in the parent CTN-0079 study in furtherance of our original overarching research question: *In settings with high need, limited resources, and differing staffing structures for managing OUD, what is the feasibility and impact of introducing a clinical protocol for OUD screening and BUP treatment initiation in the ED with referral for treatment?* CTN-0079-A1 (the "ancillary study") is an implementation study that will use mixed methods and triangulate multiple sources of data to evaluate the feasibility, acceptability, sustainability, and impact of the ED-initiated BUP clinical program and implementation facilitation strategy and identify factors influencing diffusion and effectiveness.

2.3 Primary Aims

1. Program Implementation (Evaluation of Clinical Program Reach): Over the course of the CTN-0079-A1 study, to estimate the proportion of patients receiving (i) ED-initiated/expedited BUP (primary analysis) and (ii) ED-initiated BUP (secondary analysis) amongst ED patients who are candidates for ED-initiated BUP. The composite ED-initiated/expedited BUP measure will be analyzed primarily; ED-initiated BUP will be evaluated secondarily.
2. Program Effectiveness: Amongst participants who received ED-initiated/expedited BUP over the course of the CTN-0079-A1 study, to estimate the proportion of participants: (i) with confirmed linkage to formal addiction treatment for OUD within one week, and (ii) who are confirmed to be engaged in formal addiction treatment for OUD on the 30th day following ED discharge. Engagement in treatment on the 30th day following ED discharge will be analyzed primarily; linkage will be evaluated secondarily.

Other Aims: We will also conduct several secondary implementation and effectiveness analyses as well as tertiary and exploratory analyses that include periods within the parent and ancillary studies and comparing available sources of data to further develop quality measures.

2.4 Sources of Data

1. Health record, administrative, claims, and registry data
2. Research assessments involving ED patients who are candidates for ED-initiated BUP for OUD; these assessments will document the index ED visit through the 30th day following ED discharge
3. Qualitative data (qualitative interviews, focus groups, field notes) involving ED staff, ED patients, and other stakeholders and key informants
4. Data collected through the CTN-0079 parent study
5. Qualitative data collected through CTN-0069

As in the parent study, CTN-0079, all clinical care (BUP and referral) will be delivered as part of each facility's clinical protocol, rather than as a research procedure. Implementation Facilitation (IF) activities will continue during ancillary trial preparation with a more intensive booster of IF activities occurring in the last month prior to trial commencement. Thereafter, all study IF support will cease and ancillary study data collection will begin. Data collection will occur over a course of

approximately 12 months, divided into two 6-month study periods – the Post-IF and Maintenance Periods. In accordance with the **RE-AIM framework** (Reach, Effectiveness, Adoption, Implementation, Maintenance), at minimum, a period of at least 6 months should separate the beginning of the Maintenance Period from the time of last study intervention. Study activities will be unchanged between these two periods. In this new trial, the implementation outcomes and related measurement methods have been adapted from those used in the parent study to incorporate lessons learned. Thus, primary outcome analyses will use data from the ancillary study alone. Tertiary and exploratory analyses will incorporate data from the 6-month period of patient enrollment of the parent study – i.e., the IF Period – as well as data derived from linkage to administrative databases extending over a longer timeframe (from 1 year prior to patient/participants' ED visit to 2 years following the ED visit/enrollment).

ED patients who are candidates for ED-initiated BUP (and who meet the additional study eligibility criteria to become research participants) may be enrolled as Full Study or Limited Study participants. Full Study participation involves two in-person research visits occurring ideally at the index ED visit and 30 days after ED discharge, as in the parent study. In addition, consenting participants will be asked to authorize study staff to perform a data match with health and administrative data pending data use agreements for a period beginning 1 year prior to study enrollment and ending 2 years following study enrollment. Limited Study participation will be offered to candidates who meet criteria for ED-BUP candidacy but do not meet all of the eligibility criteria (e.g., inadequate locator information) for Full Study participation. Limited Study participation includes completion of screening assessments and data matching only, without active participation in the baseline and day 30 research visits. In addition, a Waiver of Consent/HIPAA Authorization is requested to perform data matching for all adult ED patients who screen positive for non-medical opioid use during the study data collection period. Analyses will also be conducted for subgroups, including those determined to be candidates for BUP and/or receive medication for OUD, among others.

We will also recruit ED staff, patients, and other stakeholders and key informants to be participants in qualitative interviews and/or focus groups at the close of study for the purpose of learning about patient-, provider-, and organizational-level barriers and facilitators to adoption and sustainability. These data (along with qualitative data collected through CTN-0069 and CTN-0079) will provide context to study outcomes and allow us to more comprehensively address our primary research question.

3.0 INTRODUCTION

The opioid epidemic continues to ravage the country. ED visits for opioid overdose increased by approximately 30% in the brief period from July 2016 through September of 2017 in the United States (US).[1] A recent analysis of over 17,000 opioid overdose survivors found a 5% annual mortality rate and that only one in three received opioid agonist treatment subsequent to an ED visit.[2] All-cause and opioid-related mortality were reduced by 59% among patients who received agonist treatment.[2] It is imperative to maximize linkage to evidence-based care for OUD from less traditional settings such as the ED. Through a 3-arm randomized trial of 329 opioid dependent patients, D'Onofrio et al. demonstrated ED-initiated BUP with referral for ongoing BUP is superior to referral alone in engaging patients with OUD at 30 days and is cost effective.[3, 4] Despite this, few EDs have adopted this intervention. Although there appears to be momentum to address OUD in the ED, logistical barriers exist in translating research into practice.[5]

Through the NIDA CTN-0069 (Project ED Health) and CTN-0079 (ED-CONNECT) studies, we have gained invaluable knowledge about strategies to facilitate BUP initiation in the ED by conducting Implementation Science research in a total of 7 geographically diverse, academic, and community EDs serving urban and rural communities with differing levels of resources to treat OUD. CTN-0079, a multicenter implementation feasibility study, was born out of the need for timely intervention, designed to balance scientific rigor with the public health need for rapid dissemination of evidence and strategies to effectively implement BUP in EDs that are representative of where the majority of people receive care. It complements CTN-0069, a Hybrid Type 3 Effectiveness-Implementation study[6] examining the effect of IF on ED provider uptake of BUP and the effect of IF on patients' engagement in treatment in four large, urban, academic EDs.

Although the rapid timeline of CTN-0079 was of critical import, the brief period of study is not adequate to study the extent to which diffusion of the ED-initiated BUP innovation (clinical program) will occur – as time is a main element of all diffusion research. Most innovations have an S-Shaped rate of adoption with the slope of the "S" varying from innovation to innovation, across different settings, and because of a number of other potential factors.[7] For example, the curves shown in Figure 1 could represent the rate of adoption of ED-initiated BUP in different EDs and/or when different implementation strategies are employed.

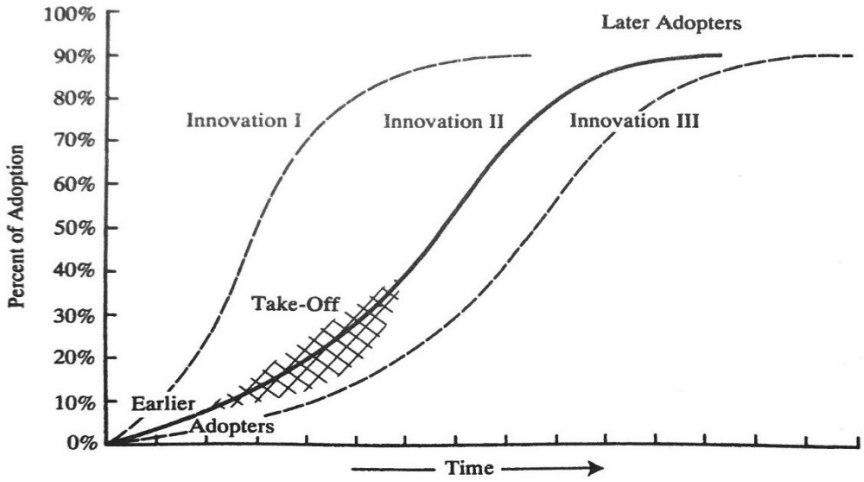

Figure 1: From Diffusion of Innovations

Prior to CTN-0079, patients presenting with OUD to its three clinical sites were not offered ED-initiated BUP. In addition to training the staff, policies, documentation templates, referral networks, and other processes needed to be developed and approved prior to implementation. Norms and system-level qualities of each context as well as the opinion leaders within each site – both supporting and opposing the intervention – have differentially impacted diffusion. Throughout implementation, sites have iteratively modified the ED-initiated BUP innovation to be acceptable to the providers and to staff adopters and suit the broader local context. By study close, we anticipate that we will have provided adequate external facilitation for meaningful adoption to take place. However, it is likely that diffusion will be somewhere in the take-off period (Figure 1) by study close, and thus, we will not know the full extent to which adoption will occur. Nor will we be able to report on sustainability or the factors influencing these outcomes.

Building on the existing infrastructure of the CTN-0079 parent study, this ancillary study will evaluate the diffusion and sustainability of the ED-initiated BUP clinical programs introduced through the parent study. This study remains well aligned with our initial **overarching research question:** *In settings with high need, limited resources, and differing staffing structures for managing OUD, what is the feasibility and impact of introducing a clinical protocol for OUD screening and BUP treatment initiation in the ED with referral for treatment?*

To accomplish this, and specifically assess sustainability at the patient, provider, and programmatic levels, we will incorporate elements of the RE-AIM framework.[8, 9] First, there will be an initial brief Implementation Facilitation (IF) booster of external facilitation to help prepare sites for their transition to independence (designate personnel, etc.) and ensure that processes are in place to allow us to collect the data we need with minimal influence on clinical activities. Thereafter, all study supported IF activities will cease. Next, using a clinical protocol adapted from CTN-0079, programmatic evaluation and patient enrollment will be extended to monitor diffusion trends and effectiveness outcomes for the next 12 months; the first six months being the post-IF period followed by six months of maintenance period (in accordance with the RE-AIM framework). We will use a mixed methods approach combining quantitative and qualitative inquiry with administrative and health record data. Qualitative inquiry of key informants (i.e., ED staff, stakeholders, patients) will occur at study close (rather than throughout patient enrollment) to minimize the potential influence on the natural course of clinical actions beyond the IF period. Lastly, in this early stage of programmatic adoption, the maintenance and growth of this clinical program will be vulnerable, particularly without ongoing support. As such, we have included an interim analysis and contingency plan to identify and respond accordingly should the program fail to be sustained (See section 5.4).

Our overarching aim is: Using mixed methods and triangulating multiple sources of data collected over the course of the parent and ancillary studies, to evaluate the feasibility, acceptability, sustainability, and impact of the ED-initiated BUP clinical program and IF strategy and identify factors influencing diffusion and effectiveness. For our primary analyses, we will evaluate program implementation via reach (i.e., proportion of candidates receiving ED-initiated/expedited BUP) and program effectiveness (i.e., proportion successfully linked to and engaged in OUD treatment). We will also conduct several secondary implementation and effectiveness analyses as well as tertiary and exploratory analyses.

Significance: It is imperative to maximize linkage to evidence-based care for OUD from less traditional settings such as the ED. It has been more than 3 years since D'Onofrio et al.'s landmark trial demonstrated the feasibility, safety, and efficacy of initiating treatment with BUP in the ED and, despite a highly visible opioid epidemic, few EDs have adopted this life-saving intervention.[3] Currently, EDs are ill-equipped to respond. Developing and refining both an intervention inclusive of OUD screening, BUP treatment initiation, and facilitated referral that is

practical for the ED as well as a pragmatic implementation strategy is critically needed. The RE-AIM framework allows the needed multi-level analysis of whether this efficacious treatment can be widely adopted and translated into meaningful outcomes in this real-world complex environment.[8, 9]

Innovation: The integration of systematic screening, BUP treatment initiation, and facilitated referral for treatment of OUD into the clinical workflow of the ED is an innovative strategy to expand access to life-saving treatment for patients with OUD. Also, it is innovative to introduce and to study this novel intervention in settings with high need, limited resources, and differing staffing structures for managing OUD, rather than focusing solely on the large academic centers where research is more often conducted. Further, we are efficiently leveraging resources, materials, and learning across these and other studies. Several design aspects are innovative and address existing gaps and criticisms of prior study. Study participation at the setting or staff level, on maintenance or sustainability, and costs, are consistently underreported in the RE-AIM literature and have been emphasized as needing attention.[9, 10] There is also an increased appreciation for the importance of context and the need for qualitative measures to help understand RE-AIM results.[9] Including these components in our study, and importantly, without interfering with the clinical workflow – minimizing the likelihood of contaminating outcomes – is innovative and will improve reporting on key issues related to implementation and external validity.[10]

3.1 Preliminary Studies – Report on the CTN-0079 Parent Study

The CTN-0079 parent study has been highly successful in achieving our overarching objectives. This expansion concept is the natural extension of our team's efforts to develop and accelerate the implementation and dissemination of best practices for treatment of OUD in general medical settings and will efficiently and expeditiously leverage the existing physical and intellectual infrastructure of CTN-0079.

Using a rigorous mixed methods and participatory action approach well-founded in implementation science, we have gained perspectives of patients, ED and community treatment providers, staff, and key stakeholders. In addition to the expected challenges, we encountered several unanticipated barriers and delays, including that all sites announced changes to their EMR systems during the study. One site changed ED staffing agencies (such that all ED providers were new), had a written policy precluding the use of BUP by ED staff, and required Catholic Church board approvals for policies. Despite these and other factors, a clinical protocol for screening, BUP treatment initiation, and referral has been implemented at each site with adoption by several unique providers from each site.

Our team has elicited a wealth of qualitative data while encountering the considerable barriers and facilitators associated with these heterogeneous contexts. We have been "on the ground" in the EDs to conduct trainings and to develop, evaluate, and iteratively refine individual- and systems-level implementation plans. The effort required to address barriers, develop and provide education/training, and to develop clinical protocols and related components has required more investigator effort and external facilitation than anticipated. Although this degree of effort may seem to point towards this program not being feasible, our effort has resulted in considerable translatable knowledge and the development of resources to support broader implementation. We have developed clinical protocols, bedside guides, EHR templates, and various training materials to support implementation and have begun to make them available online at http://www.drugabuse.gov/ed-buprenorphine and are working with the American College of Emergency Physicians (ACEP), the largest emergency medicine organization, to develop a toolkit

of resources to support dissemination and practice improvement. Most recently, our work has gained international attention through publication in the *New England Journal of Medicine*.[5]

During the drafting of this protocol, recruitment for the parent study closed. Data lock recently occurred for formal analyses and reporting. The number of patients who received ED-initiated BUP has surpassed our original estimates. Importantly, without study intervention, the number of patients receiving BUP would be zero. Prior to CTN-0079, none of its clinical sites offered ED-initiated/expedited BUP or even formal processes to identify patients with non-medical opioid use. For the main secondary outcome of engagement in treatment at 30 days, we did not reach our original recruitment target of 60 patient-participants or the subsequently raised targets. Through the ancillary study, we should be able to achieve the necessary sample size to evaluate impact more robustly than originally proposed in the parent study. Also, we have identified and addressed several factors contributing to recruitment challenges. For example, we expanded our operating definition of “eligible and willing to receive ED-initiated BUP” to include patients for whom these criteria could be inferred reasonably through such documentation in the patient’s medical record to address the aforementioned differences in clinical and research terminology. In this new study, we will incorporate these and other lessons learned, which should boost enrollment and the completeness and quality of data capture.

4.0 AIMS AND OBJECTIVES

4.1 Overarching Aim

Using mixed methods and triangulating multiple sources of data collected over the course of the parent and ancillary studies, to evaluate the feasibility, acceptability, sustainability, and impact of the ED-initiated BUP clinical program and implementation facilitation strategy and identify factors influencing diffusion and effectiveness.

4.1.1 Primary Aims

1. Program Implementation (Evaluation of Clinical Program Reach): Over the course of the CTN-0079-A1 study, to estimate the proportion of ED patients receiving (i) ED-initiated/expedited BUP and (ii) ED-initiated BUP treatment amongst ED patients who are candidates for ED-initiated BUP. The composite ED-initiated/expedited measure will be analyzed primarily; ED-initiated BUP will be evaluated secondarily.
2. Program Effectiveness: Amongst participants who received ED-initiated/expedited BUP
    a. To estimate the proportion of participants with confirmed linkage to formal addiction treatment for OUD within one week following ED discharge (operationalized as within 7-10 days);
    b. To estimate the proportion of participants who are confirmed to be engaged in formal addiction treatment for OUD on the 30th day following ED discharge.

    Engagement in treatment on day 30 will be analyzed primarily; linkage will be evaluated secondarily.

4.2 Secondary Implementation Aims

1. To estimate the rates of ED-initiated/expedited BUP provided via the ED over the course of the CTN-0079-A1 study with rates of ED-initiated BUP provision estimated secondarily.
    a. To compare rates of BUP provision between the Post-IF and Maintenance Periods, including each time BUP is provided and BUP provision among unique individuals among denominators of 30-day and 6-month periods of time;
2. To generate diffusion curves in which the number of patients provided BUP is displayed graphically as a function of time (30-day periods).
3. To evaluate provider adoption as measured by the number and proportion of ED providers who have: (a) provided BUP treatment and (b) completed DATA 2000 training to become a BUP prescriber.
4. To generate proportions for the completion of critical actions and other components of the ED-initiated BUP clinical program.

4.3 Secondary Effectiveness Aims

1. To evaluate patient-level outcomes 30 days after ED discharge and changes from pre-IF among CTN-0079-A1 study participants who received ED-initiated/expedited BUP, including non-medical opioid and other drug use (self-report using TLFB; urine toxicology), healthcare utilization, quality of life, and other patient-reported outcomes (PROMIS-29, PHQ-9, Treatment Effectiveness Assessment (TEA), treatment satisfaction, risk

behaviors, overdose events, and other drug-related consequences).

a. Secondary analyses will evaluate the participant subgroups who received ED-initiated BUP and ED-expedited BUP separately as well as those who did not receive BUP.

All the above secondary effectives analyses will be performed for Full Study participants. Additional secondary analyses for limited study participants will be performed for available effectiveness outcome measures, as listed in the table of assessments.

4.4 Tertiary and Exploratory Aims

1. To evaluate implementation and effectiveness outcomes over the course of the CTN-0079 parent and CTN-0079-A1 ancillary studies and conduct comparisons between each of the defined 6-month Implementation (i.e., parent study), Post-IF, and Maintenance Periods for which comparable data exists.
2. To further develop meaningful quality measures related to the recognition and treatment of OUD in the ED to support data harmonization and the use of valid, reliable, comprehensive, and useable measures in future research and clinical performance monitoring and standards by:
    a. Testing permutations of the implementation and effectiveness outcomes, by:
        i. Evaluating permutations of how the numerator and denominator are defined and how these data are collected for the primary implementation outcome;
        ii. Evaluating different timeframes of assessment (e.g., 72 hours, 14 days) and including a time-to-event for the primary effectiveness outcomes (i.e., linkage to and engagement in treatment), and exploring alternate means of how these data are captured and defined (e.g., claims and other administrative data).
    b. Comparing the agreement of quality measures assessed using administrative data to the gold standard data collected through the clinical trial research assessments.
    c. Identifying patient-level characteristics as well as structural and process measures associated with measure completion and effectiveness.

5.0 STUDY DESIGN OVERVIEW

5.1 Overview

The ancillary study will use mixed-methods combining quantitative and qualitative inquiry (interviews/focus groups and field notes) with administrative and health record data with some analyses including data collected from the parent CTN-0079 study. Further, qualitative data will be analyzed in the context of themes derived from CTN-0069 and CTN-0079. CTN-0079-A1 is planned to be conducted at the same three sites of the parent study: (1) Catholic Medical Center, Manchester, NH; (2) Valley Regional Healthcare, Claremont, NH; (3) Bellevue/NYC Health and Hospitals, New York, NY. Many of the methods, operating procedures, measures and forms will be retained or adapted from the parent study. However, CTN-0079-A1 is a new study in which lessons learned through the parent study have informed important design modifications necessary to improve study rigor and utility.

In CTN-0079, we employed a multi-faceted participatory action research approach and IF to develop, implement, and iteratively refine site-specific clinical protocols and implementation plans to screen and assess for OUD and, when appropriate, initiate BUP and referral for ongoing treatment. Data were collected from a variety of sources and in a number of ways. To learn about feasibility and acceptability, including barriers, facilitators, and other needs to support implementation, we conducted key informant interviews and focus groups to learn about the perspectives of various stakeholders. To assess adoption of the clinical protocol and fidelity to the critical components of its delivery, we abstracted data from the medical record and associated records. Also, we enrolled participants who were determined to be eligible for and willing to receive ED-initiated BUP (both those who received BUP and those who did not) to participate in assessments following their index ED visit to explore patient-level outcomes and learn about barriers and facilitators encountered during or associated with their actual experience in the ED.

In the ancillary study, there will be three phases of participation: 1) candidates for ED-initiated BUP will be enrolled over a 12-month period to participate in two research visits (Days 0 and 30) and/or authorize administrative data matching, 2) ED staff, patients, and stakeholders will participate in semi-structured qualitative interviews/focus groups at study close, and 3) retrospective chart review and data matching for all adult ED patients identified to have non-medical opioid use presenting to the ED during the IF, Post-IF or Maintenance periods. The study will be conceptualized using the RE-AIM framework.

As the parent study comes to a close and while we finalize preparations for the ancillary study (e.g., obtain regulatory approvals, finalize data collection procedures, etc.), we will synthesize the quantitative and qualitative data collected thus far, identify existing needs, and develop and execute a plan to support implementation and sustainability at the sites. The final month of this IF period (the IF “booster”) will involve more intensive external facilitation. This IF booster will mark the end of study intervention/support and the end of the IF Period and the beginning of the ancillary study. At that time, data collection for the primary outcome and participant enrollment will begin and continue for a period of 12 months divided into two 6-month periods – Post-IF and Maintenance Periods. The Post-IF and Maintenance Periods are identical in terms of study activities. They are differentiated only by the 6-month minimum interval of time following the cessation of study support that must pass to evaluate maintenance or sustainability in accordance with the RE-AIM framework. Upon completion of 12 months of participant enrollment, we will recruit ED staff, patients, and other stakeholders and key informants to participate in qualitative interviews and/or focus groups at the close of study for the purpose of learning about patient-, provider-, and organizational-level barriers and facilitators to implementation and sustainability.

These data (along with qualitative data collected through CTN-0069 and CTN-0079) will provide context to study outcomes and allow us to more comprehensively address our primary research question.

5.2 Table 1: Description of Study Periods Spanning CTN-0079 and CTN-0079-A1

Period	Study	Description
Pre-Implementation Period	CTN-0079	Preceded CTN-0079 data collection and ended upon approval of ED-initiated BUP clinical protocols at the clinical sites. During this time, BUP was not initiated in the ED sites (to any meaningful extent) and participants were not enrolled (except for qualitative inquiry).
Implementation Period (IF Period)	CTN-0079 to CTN-0079-A1 (all enrollment during parent study)	Initial period of program adoption – when clinical protocols were first approved and introduced at ED sites and supported by study-supported IF – and will extend into CTN-0079-A1. This period marked the beginning of the 6-month period of data collection for the parent study (10/2018 - 5/2019). Limited IF activities will continue after the parent study as CTN-0079-A1 preparations are finalized and approved. Post IRB-approval, a one-month intensive IF Booster will mark the end of all study supported intervention/IF and the IF Period.
Post-IF Period	CTN-0079-A1	During this time, there will be no study IF support. Data abstraction and participant enrollment will occur during this 6-month period.
Maintenance Period	CTN-0079-A1	A 6-month period of data collection immediately following the Post-IF Period to evaluate the extent to which the ED-initiated BUP program becomes a part of the routine organizational practices. No IF support or study intervention will occur during the Maintenance Period. At the conclusion of the Maintenance Period, study staff will conduct close-out qualitative interviews and focus groups with ED staff, patients, and stakeholders, provide/receive feedback, and provide final IF. Note: If IF activities are resumed due to failure of the ED-initiated BUP clinical program to be maintained, by definition, this will no longer constitute a Maintenance Period (as described in the Contingency Plan, section 5.4).

5.3 Study Procedures Overview

As in the CTN-0079 parent study, all clinical actions of the ED-initiated BUP clinical program, including screening, assessment, medication initiation, and referral for ongoing treatment, will be delivered as a clinical procedure, rather than by the research team. Consenting patients who are candidates for ED-initiated BUP who meet additional eligibility criteria (see section 7.2 and 7.3) will be recruited by research staff to participate in two research visits; ideally, the first will occur during the index ED visit and the second will occur on the 30th day following ED discharge. Consenting Full Study participants will also be asked to authorize study staff to perform a match with health and administrative data to further assess implementation and

effectiveness outcomes one year prior to study enrollment and extending for up to two years post study enrollment. All Full Study participants will be required to participate in data matching; however, they will have the opportunity to opt out of releasing retrospective data prior to study enrollment. Limited Study participation will be offered to ED-BUP candidates who do not meet all eligibility criteria for Full Study participation (e.g., inadequate locator information; unwilling to participate in research visits). Limited Study participation will be limited to data matching only without active participation in the baseline and day 30 research visits. The clinical care of patients enrolled in either the Full or Limited Study will not be affected.

Candidacy for ED-initiated BUP will serve as the initial criteria for determining a patient's potential study eligibility, as well as for the denominator of the primary implementation outcome. This terminology differs from the terminology of "eligible and willing to receive ED-initiated BUP" used in the parent study for the aforementioned reasons and lessons learned through the parent study. In brief, any patient who would have met the eligibility criteria as defined in the parent study will be eligible in the ancillary study as will patients identified to have nonmedical opioid use without explicit documentation or evidence of contraindications to treatment. To be eligible for research participation, all criteria used to determine one's eligibility and willingness to receive ED-initiated BUP must be satisfied as confirmed through research staff assessments or sufficient EMR documentation. The eligibility criteria are discussed in greater detail in sections 7.2 and 7.3. The means of identifying candidates for ED-initiated BUP will include the medical record abstraction procedures used in CTN-0079. In addition, using methods adapted from CTN-0069, research staff will identify potential participants by assessing them directly via conducting health surveys. (Study entry procedures are discussed further in section 9.0.) The ED Health Survey has questions related to eligibility (for both ED-initiated BUP and study participation) embedded within general public health screening questions. Although this research assessment (the ED Health Survey) will be used primarily for recruitment purposes, all patients with OUD identified through this research assessment will be given an informational pamphlet. This minimal clinical intervention (health quiz and pamphlet) is unlikely to have a substantive effect on outcomes or to influence clinical procedures associated with the delivery of the ED-initiated BUP program. Importantly, research staff will not communicate responses to the ED Health Survey to clinical staff. The study purpose will be described as a study to evaluate outcomes among ED patients with OUD (section 12.0).

5.4 Contingency Plan

If we conclusively determine that the ED-initiated BUP program is not sustained at one or more ED sites via interim analysis, we will declare this outcome (i.e., failed sustainability). Rather than ending the study at this point for the affected site(s) and/or observing the continued failure, we will use this as an opportunity to learn about why the failure occurred and attempt to restore programmatic adoption. Investigators will return to the sites to conduct interim focus groups and/or interviews and IF activities will resume (i.e., a second IF booster). Participant enrollment and data collection will continue throughout the planned study timeline. By definition, site(s) receiving additional support will no longer enter or be in the Maintenance Period and will not be considered for outcomes involving sustainability and maintenance but may be considered for some exploratory outcomes. Statistical analyses and reporting would be amended accordingly with appropriate sensitivity analyses. We decided to include this contingency plan given the gravity of the epidemic and urgent need for data to guide approaches as well as the potential learning opportunity the added inquiry and intervention may afford.

5.5 Interim Analysis and Criteria for Failed Sustainability

We will conduct an interim analysis for each site at the conclusion of the Post-IF Period to determine if the study should proceed at each site as planned – without additional IF support – into the Maintenance Period. For this analysis, we will compare the rate of ED-initiated BUP during the 6-month periods of enrollment occurring during the IF Period of the parent study and the Post-IF period of the ancillary study (i.e., the number of patients receiving ED-initiated BUP divided by a denominator of 6 months). Note that this calculation is based on medical record abstraction, and not assessment data collected from enrolled participants. For this analysis, the ED-initiated BUP measure will include ED-initiated BUP (administered or prescribed) without inclusion of ED-expedited BUP (warm handoffs to BUP treatment within 24 hours), as data for the later measure was not formally collected in the parent study. Sustainability at the site will be declared to have failed if the treatment initiation rate in the Post-IF period is <25% of that observed during the IF Period, with the qualification that ED-expedited BUP does not become a primary means of treatment for a site, such that inclusion of this outcome would significantly affect the analysis and change the conclusion.

5.6 Data Matching and Linkage to Administrative Data

Administrative data refers to information that is collected, processed, and stored in automated information systems. Administrative data include medical plan enrollment or eligibility information, claims information, and managed care encounters. The claims and encounters may be for hospital and other facility services, professional services, prescription drug services, laboratory services, etc.[11]

Using administrative records data and survey/participant data to enhance each other offers enormous potential for scientific and policy-related research. The improved availability of data sources and progress in data-matching technology have expanded the potential for creating such linked data. Provision of administrative data for scientific research reflects a cost-effective way of complementing the primary study data as these data are already being collected for administrative purposes. Linking administrative records data with participant level assessment data helps to overcome the shortcomings of administrative data by enhancing the usually limited set of information recorded. [12]

Unfortunately, the current clinical data research infrastructure does not allow for leveraging existing data streams accurately. Fragmented health systems, the lack of interoperability between clinical and research systems, and need for EHR phenotypes that better characterize patients with opioid-related presentations are among the current barriers. The value of EMR data to track ED patient activity is further compounded by the fact that, unlike most other clinical settings, continuity of care with a provider or within a health care system is not expected for ED patients. Further, there are added privacy concerns and restrictions accessing substance use data. That being said, members of our team are involved in CTN-0081 and other initiatives to swiftly find solutions to this problem.

In CTN-0079-A1, we will collect a data set of patient data to permit linkage to administrative data for the purpose of quality measurement and performance monitoring that is more feasible and sustainable (less labor intense) for broader generalization. Included in this data matching will be patients who enroll in either the Full or Limited Study as well as all adult ED patients screening positive for non-medical opioid use during the Post-IF and Maintenance periods for whom there is adequate identifying information available to permit matching. Similarly, we will draw on the data set generated for patients who presented during CTN-0079 to perform data matching for all adult ED patients identified to have non-medical opioid use during the CTN-0079 IF period for

whom there is adequate identifying information to permit matching. We request a Waiver of Consent/HIPAA Authorization to access this patient information.

Administrative data matching will allow us to evaluate outcomes for the larger population of patients who present to the ED with OUD. It is essential to evaluate the entire population of patients with opioid use to ensure equity in the larger effort to improve quality of care and treatment outcomes at the population level. For several reasons, many of the most at-risk individuals who are less likely to access health services are also less likely to become research participants (e.g., those who lack phone access or home address, lack social contacts for locators, or who present the ED overnight or outside of conventional business hours). Therefore, these subgroups are not equitably represented in the research and may not expect the same potential future benefits that result from it. This administrative data match conducted through a waiver of consent will mitigate this problem. As we have learned in CTN-0079 and other studies, it is not feasible to contact the large volume of patients treated in the ED to obtain individual authorizations, particularly among the aforementioned individuals without stable phone access or addresses. Through a waiver of consent and in accordance with safeguards to be outlined in pending data use agreements, we will share a data set with the covered entity that is the owner/custodian of the administrative data. This effort is well-aligned with our overall goal to inform the development and improve the effectiveness and reach of programs that identify and initiate treatment of OUD in EDs in a way that is generalizable to support population-level health quality improvement and treatment outcomes.

One way that we will leverage existing data streams will be to compare the data collected through participant enrollment to the data capture that would have been possible had we not enrolled patients (other than to obtain their authorization health record and administrative data review). For example, we will review the prescription drug monitoring program (PDMP) database to determine if and when patients/participants filled a prescription for BUP following their index ED visit. This example also demonstrates the shortcomings of relying on individual sources of data, as the PDMP does not include medication administration in an Opioid Treatment Program (OTP) or inpatient settings. Thus, this work is exploratory and will help inform the development of future studies and quality measures.

Data of particular interest: Means of collecting data related to health services utilization (ED visits, hospitalizations, ambulance use, as well as associated costs), include through the EMR and linked EMR data, direct contact with treatment providers, health claims data, Fire Department and Emergency Medical Services (EMS) databases, state drug and alcohol treatment services databases, and other sources. We will also explore means of confirming subsequent OUD treatment and receipt of MOUD, including though the use of the PDMP, claims, and state drug and alcohol treatment services databases. Other data of interest include, but are not limited to, state vital statistics data and Medical Examiner's data (overdose- and all-cause mortality), law enforcement databases (arrests/incarcerations), EMS data (ambulance use and overdose events). These administrative data would also inform potential cost analyses.

In both New Hampshire and New York, there are ongoing efforts to create an integrated data warehouse and data analytics platform. These systems allow for data from disparate data systems in their respective states to be integrated into a common data framework. The New Hampshire data systems include 25 data sets, including All Payer Claims Data (APCD) and other health data, Department of Health and Human Services (DHHS), and law enforcement data. Similarly, the NYC system will integrate a wide array of state government data datasets. Our team will work with relevant stakeholders with a focus on the NH Department of Health and Human Services (DHHS) and the NYU Health Evaluation and Analytics Lab (HEAL) to execute data use agreements as we hope to utilize these robust, more efficient emerging resource and/or other

administrative data. Description of the types of data will be included in the informed consent processes for study participation.

While we hope to be able to execute data use agreements for data linkage, we cannot guarantee this permission will be granted. If permitted, individual-level data with direct identifiers will only be accessible under the restrictions of the pending data use agreement. Because direct identifiers are not always perfect, probabilistic matching will also be used when direct matching fails to maximize the linkages across data sources. After the data are linked, they will then be sharable within direct patient identifiers with others including data analysts, statisticians, and economists who will be preparing data for analyses and conducting analyses.

6.0 ESTIMATED PROJECT TIMELINE

The planned overall study period is 24 months, including study start up, IF booster, data collection, data matching, analysis, and reporting.

6.1 Table 2: Estimated Project Timeline

	Study Month						
	1-3	**4-5**	**6**	**7-12**	**13-18**	**19-21**	**22-24**
Study Preparation							
PRB Approval							
MOP, training development							
Data systems, eCRF development							
Train site research teams							
Regulatory approvals							
Implementation Facilitation							
EMR data abstraction			(Pilot)				
Participant enrollment and follow-up							
Data matching							
Qualitative interviews and focus groups							
Analysis and Reporting							
Data cleaning and data lock							
Data analysis							
Final study report and dissemination							

IF and support will continue for the sites during study development and start up. We are developing systems to retrospectively collect data on provision of BUP for the period of time between the parent study and the ancillary study. Prior to data collection, site teams will begin piloting data abstraction and approximately one-month of IF will commence to ensure that all clinical protocols, resources, and EMR programming is in place. Participant recruitment will begin once IF is complete and will take place over approximately 12 months, spanning a post-implementation period of six months and a maintenance period of six months. Full Study participants will complete a follow-up visit to assess engagement in treatment on the 30th day following ED discharge. The Day 30 follow-up visit will ideally occur no more than 7 days after this target, although outreach to reengage participants lost to contact may continue past this point. Data matching for the Limited Study participants will focus on the first 30 days following the index ED visit with evaluation continuing up to two years following study enrollment. Access to retrospective data one year prior to study enrollment will also be requested but will be optional.

7.0 STUDY POPULATION

The study population includes 4 sub-samples.

1. Qualitative: Stakeholders within and outside the hospital, including ED providers, hospital leadership, ED patients, ED staff, and community opinion leaders will be recruited to participate in the IF booster and qualitative focus groups and interviews.
2. ED patient process and outcome measures (administrative and health record data): Administrative and health record data for all adult ED patients will be examined to assess rates of screening, assessment, BUP eligibility determination, and other process measures. Further review of health records and administrative data matching to assess process/outcome measures (e.g., claims to assess linkage to treatment or filled prescriptions) will be performed in ED patients over the age of 18 screening positive for non-medical opioid use via a Waiver of Consent.
3. Full Study (Research visits): ED patients who are candidates to receive ED-initiated BUP and who meet additional study participation eligibility criteria (described below) will be recruited to participate in two research visits (at baseline and Day 30) and data matching.
4. Limited Study (Data matching only): ED patients who are candidates to receive ED-initiated BUP and who meet additional study participation eligibility criteria (described below) but who are unable or unwilling to participate in the Full Study will be invited to provide authorization for health services review and data matching with available registry, claims or administrative data.

7.1 Qualitative Population Eligibility Criteria

7.1.1 Inclusion Criteria

1. Be a key stakeholder or opinion leader for ED-initiated BUP at the hospital site or in the community, including but not limited to ED staff, ED patients, hospital leadership or community members.
2. 18 years of age or older.

7.1.2 Exclusion Criteria

1. Unwilling or unable to provide consent.
2. Currently in jail, prison or any inpatient overnight facility as required by court of law or have pending legal action or that could prevent participation in the study.

We estimate that approximately 24 stakeholders (approximately 8 at each site) will participate in interviews or focus groups at study close.

7.2 Full Study Population Eligibility Criteria

7.2.1 Inclusion Criteria

1. 18 years of age or older
2. Be able to speak English sufficiently to understand study procedures
3. Be a potential candidate for ED-initiated BUP by meeting either of the following two criteria:

a. Clinical determination: Clinical documentation indicating the patient is a willing and eligible candidate for ED-initiated BUP or for whom this can be reasonably inferred, including any patient who receives ED-initiated BUP (via direct administration, prescription, or direct referral/transfer to BUP provider within 24 hours of ED discharge).

b. Research determination: Both a and b below must be true at the time of study enrollment:

   a) Assessment conducted by an RA indicates that the patient- (all must be true):

      i. has had nonmedical opioid use within the last 7 days,

      ii. meets DSM-5 criteria for moderate or severe OUD,

      iii. denies methadone use within 72 hours of ED visit registration,

      iv. is not engaged in formal MOUD treatment,

      v. is not prescribed opioids for chronic pain management,

      vi. reports being interested or "not sure" if interested in receiving BUP as elicited on the ED Health Survey during the index ED visit.

   b) Absence of clinical documentation associated with the ED visit indicating that the patient is not a candidate for ED-initiated BUP.

7.2.2 Exclusion Criteria

1. Unwilling or unable to provide written informed consent/HIPPA Authorization for research procedures and/or consent for the release of health records and data matching for a period of 2 years following enrollment. Note that participants may opt-out of authorization for the 1 year prior to enrollment.
2. Currently engaged in formal MOUD treatment at the time of index ED visit.
3. Currently in jail, prison or any inpatient overnight facility as required by court of law or have pending legal action or that could prevent participation in the study.
4. Previous participation as a patient-participant in CTN-0079 or previous participation as a Full Study participant in the current study (Note: prior participation in Limited Study or qualitative inquiry does not preclude a patient from enrolling as Full Study participant.)
5. Presents from a medical-based extended care facility (e.g., skilled nursing facility)
6. Current research participant in a substance use intervention study.
7. Inadequate locator information (unable or unwilling to provide two unique means of contact).
8. Unable or unwilling to complete research visits at baseline and Day 30.

We anticipate that approximately 120 Full Study participants (approximately 40 per site) will be enrolled to complete research assessments and data matching within the 12-month recruitment timeline. We anticipate that as many as an additional 200 ED-BUP candidates will enroll in the Limited Study for a total N=320 for data matching outcomes.

7.3 Limited Study Population Eligibility Criteria

7.3.1 Inclusion Criteria

Inclusion criteria is the same as inclusion criteria above, for the Full Study. See section 7.2.

7.3.2 Exclusion Criteria:

1. Unwilling or unable to provide written agreement/HIPPA Authorization to participate and/or consent for the release of health records and data matching for a period of 2 years following enrollment. Note that participants may opt-out of authorization for the 1 year prior to study enrollment.
2. Currently engaged in formal MOUD treatment at the time of index ED visit.
3. Currently in jail, prison or any inpatient overnight facility as required by court of law or have pending legal action or that could prevent participation in the study.
4. Previous participation in the current study as a Limited Study or Full Study participant (Note: prior participation in qualitative inquiry does not preclude a patient from enrolling).
5. Presents from a medical-based extended care facility (e.g., skilled nursing facility).

7.4 Study Sites

The study is planned to be conducted in the three Emergency Departments that participated in the parent protocol:

1. Valley Regional Healthcare, Claremont, NH
2. Catholic Medical Center, Manchester, NH
3. Bellevue Hospital Center, New York, NY

For each site, clinical procedures including screening, BUP treatment initiation, and referral to ongoing care were approved and implemented between September - October of 2018.

8.0 STUDY OUTCOMES

Using mixed methods and triangulating multiple sources of data collected over the course of the parent and ancillary studies, we will evaluate the feasibility, acceptability, sustainability, and impact of the ED-initiated BUP clinical program and implementation facilitation strategy and identify factors influencing diffusion and effectiveness. Converging provider and patient perspectives and field notes with process measures and intervention outcomes, including proportions screened, treated, and engaged in treatment, will provide explanation to contextualize and better understand feasibility, acceptability, and factors associated with the rate with which the ED-initiated BUP innovation is adopted and how well it is sustained. Using directed content analysis, the qualitative interviews in conjunction with the qualitative inquiry conducted through CTN-0069/0079 and the patient-level factors and the granular level of data to be collected will allow us to better identify data pointing to the subgroups and specific stages of intervention where gaps exist as well as protective measures.

8.1 Primary and Key Secondary Outcomes

We have two primary outcomes to assess (1) clinical program implementation reach and (2) program effectiveness.

8.1.1 **Program Implementation** (Evaluation of Clinical Program Reach)

The primary implementation outcome is the proportion of patients receiving (i) ED-initiated/expedited BUP (primary analysis) and (ii) ED-initiated BUP (secondary analysis) amongst patients who are candidates to receive ED-initiated BUP.

Rationale: Our primary outcome is a measure of the success of a clinical protocol for identifying nonmedical opioid use and initiating treatment with BUP either directly through administration or prescription (i.e., ED-initiated BUP) or indirectly through transfer of care via “warm” referral to be seen within 24 hours for BUP treatment (i.e., ED-expedited BUP). We will conduct separate analyses for the composite measure of ED-initiated/expedited BUP and ED-initiated BUP (rationale discussed below). The efficacy of BUP is well-established across several domains including drug use, overdose, societal costs, quality-of-life and adherence to other ongoing treatments, e.g., for HIV. The ED is a meaningful setting in which to initiate treatment. The prevailing culture of the ED is that SUD is a non-emergent, chronic condition better addressed outside the ED where time and resources are less limited. Rarely do any components of Screening, Brief Intervention (whether brief advice, brief intervention, or initiation of treatment), or Referral for Treatment occur. Screening itself is not included in the clinical protocol elements of the largest emergency medicine organization, the American College of Emergency Physicians (ACEP), which are followed by over 200 healthcare systems. For these reasons, we have chosen to quantify rates of BUP initiation in the ED for the primary outcome and to evaluate downstream patient-level outcomes secondarily.

Description of the Measure and Methods:

- Receipt of ED-initiated/expedited BUP and Receipt of ED-initiated BUP (numerator) will be operationally defined to include: (1) administration of BUP in the ED, (2) prescription for BUP as part of the ED visit, or (3) provision of a specific “warm” referral or transfer of care to a provider, clinic, or treatment setting with the capacity to administer or prescribe BUP within no more than 24 hours. This measure will be abstracted from the health record primarily.

- Rationale: Adding ED-expedited BUP reflects contextual differences impacting the mode of treatment delivery identified through CTN-0079 (and, through informal comparison to CTN-0069 implementation trends). In large academic settings, the model appears to center on providers becoming BUP prescribers (i.e., obtaining DATA 2000 X-waiver). In some community ED settings (including sites outside of CTN-0079), however, particularly those with locum tenens staffing models, this model is less acceptable and less feasible. Instead, the emphasis often shifts from getting providers X-waivered to setting up streamlined, low barrier referral networks with urgent appointment availability. The addition of warm handoff for BUP treatment within 24 hours represents a patient-centered and context-centered good outcome for patients who are not yet in opioid withdrawal—as most ED providers do not have DATA 2000 X-waivers to prescribe BUP—and it is generally not acceptable (from the hospital, provider, and potentially the individual patient perspectives) to prolong patients' ED visit for the hours that may be necessary for an adequate state of opioid withdrawal to manifest so that BUP may safely be administered. As such, measures of quality that do not include ED-expedited BUP would not only miss this positive outcome but also potentially result in reduced performance and penalization related to contextual factors that may be outside of the control of the ED. The separate analysis of ED-initiated BUP (without ED-expedited BUP) is important to support harmonization of data to permit comparisons across studies in which this outcome is used, including CTN-0079. Also, ED-initiated BUP and ED-expedited BUP may not have equivalent effects on outcomes. Further study is needed to assess the potential differential impact the modes of treatment delivery have on outcomes.
- Operationally, ED-expedited BUP is a warm hand-off to a provider who can provide (dispense and/or/prescribe) BUP within 24 hours of discharge from the ED. To be included, there must be confirmation of this handoff, inclusive of clinical documentation in the EMR of medical decision making indicating that the patient is being handed off/referred for BUP treatment to a specific provider, clinic, or service with the capacity and availability to provide BUP within 24 hours of the patients' ED discharge. This could include a patient being given an appointment at a specific time and location, transfer to a provider, facility, or inpatient service directly from the ED, or through a pre-arranged follow-up mechanism in which a treating provider/facility has agreed to accept patients referred from the ED. Such agreements often exist to ensure access to urgent follow up care after ED discharge (for other medical problems and, more recently, OUD) as it may not be practical or possible to schedule appointments, particularly outside of traditional business hours. Neither confirmation of a completed appointment (i.e., patient shows up and is seen) nor receipt of BUP at the dedicated follow-up appointment will be required as privacy regulations may preclude our obtaining these data and as the patient and treating provider may elect to treat with alternative regimes (e.g., methadone, naltrexone).
- Candidate for ED-initiated BUP (denominator): In the parent study, the denominator included patients with clinical documentation of non-medical opioid use and documentation: (a) affirming eligibility and willingness to receive ED-initiated BUP (or for whom this could be reasonably be inferred) or (b) confirming receipt of BUP administered or prescribed as part of the ED visit. For the ancillary study, we will include all patients identified to have non-medical opioid use and exclude only those for whom there is documentation or other evidence of the patient *not* being eligible or willing to receive ED-initiated BUP (or for whom this could be reasonably be inferred). Rationale: The rationale for this change is that it should provide more complete capture (expect higher sensitivity and lower specificity) and hold the sites more accountable for ensuring

complete clinical documentation. All patients identified to have non-medical opioid use will be assumed to be candidates for ED-initiated BUP unless there is documentation indicating otherwise. In this way, inadequate documentation would be more likely to dilute positive outcomes rather than strengthen them. This outcome is somewhat analogous to a metric used as a Centers for Medicare and Medicaid Services (CMS) accountability measure of quality for treatment of pneumonia in EDs – the proportion of patients who receive antibiotic treatment for pneumonia within 4 hours of ED triage. The denominator includes all patients with diagnosis of pneumonia and excludes only patients for whom specific documentation exists indicating why antibiotics were not administered within 4 hours (e.g., patient refused, atypical presentation delaying diagnosis, etc.).

- Patients may be identified as candidates for ED-initiated BUP through EMR abstraction and/or through RA assessments embedded in health surveys using methods adapted from CTN-0069. This represents a change from the parent study, which was limited to EMR abstraction. RAs will approach patients in the ED to conduct health surveys embedded with questions to screen for non-medical opioid use and, if positive, assess for the main criteria for establishing one's eligibility and willingness to receive ED-initiated BUP (i.e., untreated, moderate to severe OUD; opioid use within 7 days; absence of common contraindications; interest in BUP treatment – as per section 7.2). Specific criteria of how to reconcile discrepant EMR and RA obtained data will be outlined in the MOP. Rationale: This additional means of identifying patients who are potentially eligible for ED-initiated BUP (and subsequent enrollment) will allow us to identify the target population in the event of diminished fidelity to clinical screening for non-medical opioid use. Further, we will use these data for quality assurance of clinical screening and secondary clinical assessments.

8.1.2 Program Effectiveness

Amongst participants who received ED-initiated/expedited BUP enrolled in 0079-A1:

1. with confirmed linkage to formal addiction treatment for OUD within one week following ED discharge (operationalized as within 7-10 days)
2. who are confirmed to be engaged in formal addiction treatment for OUD on the 30th day following ED discharge

Engagement in treatment on day 30 will be analyzed primarily; linkage will be evaluated secondarily.

Rationale: Initial treatment linkage and engagement at Day 30 are our primary program effectiveness outcomes. We include linkage to treatment, in part, because factors outside of the ED visit may be attributed to the 30-day engagement outcome. However, as the primary outcome measure of the original D'Onofrio study and CTN-0069, and the most important secondary outcome of CTN-0079 and its use in other planned studies, 30-day engagement appears to be emerging as a preferred effectiveness measure. We are also evaluating initial linkage to treatment. We feel these are both important and a good compromise when considering that others argue for long-term outcomes (e.g., 12 month). Further support of this quality measure is that engagement in treatment is associated with other long-term patient outcomes of interest related to morbidity and mortality. Also, 30-day outcomes are a common metric in ED research and clinical quality measurement (e.g., 30-day hospital readmissions, mortality).

Collecting these data across the parent and ancillary studies will likely increase the precision of our estimate and contribute to the limited data we currently have on this outcome, which includes

the 78% rate observed in the original D'Onofrio efficacy trial and a notably lower rate observed in real-world clinical practice. According to unpublished raw data from Andrew Herring, MD, linkage to treatment has been observed in approximately 30-40% of patients in California's ED-BRIDGE program. This discrepancy in treatment engagement after ED discharge strongly supports our further investigation of effectiveness outcomes without the heavily supported conditions present in efficacy trials.

Measure description: The treatment linkage/engagement measure must be confirmed by direct contact with the facility and/or treating clinician or other objective means (e.g., medical record review). Linkage to treatment for OUD will be defined as attendance at formal addiction treatment following the ED visit. Engagement in treatment for OUD will be defined as enrollment in formal addiction treatment on the 30th day following ED discharge. Formal addiction treatment will be those treatments consistent with the American Society of Addiction Medicine's (ASAM) level of care (1-4) and will include a range of clinical settings, including office-based providers of BUP or naltrexone, OTPs, intensive outpatient, inpatient, or residential treatments.

8.2 Secondary Outcomes

Secondary Implementation outcomes will include other measures of reach, including evaluating ED-initiated BUP as a function of time. Other RE-AIM model dimensions to be assessed include Adoption (the proportion of providers who deliver ED-initiated/expedited BUP) and Implementation fidelity (proportions for adherence to clinical actions associated with the delivery of ED-initiated BUP). Maintenance will be assessed by evaluating these patient- and setting-level outcomes ≥ 6 months after the cessation of all study-supported IF (i.e., the Maintenance Period). As in the parent study, a range of secondary effectiveness measures will be assessed at the index ED and Day 30 visits for Full Study participants only, including but not limited to:

- Self-reported days of opioid and other drug use (TLFB)
- UDS results at 30 days post index ED visit
- Overdose events
- Healthcare utilization
- Quality of Life, Health, and Treatment Effectiveness (PROMIS-29, PHQ-9, TEA)
- Treatment satisfaction and acceptability

Process measures related to the clinical protocol include but are not limited to:

- Proportion of ED patients triaged who are screened for non-medical opioid use
- Proportion of patients screened who are positive for non-medical opioid use
- Among those positive:
    - Proportion of patients who are candidates to receive ED-initiated BUP
    - Proportion of patients who receive ED-initiated BUP (and the means of delivery, i.e., direct administration, prescription, or indirectly via warm referral within 24 hours)
    - Number meeting inclusion/exclusion criteria for ED-initiated BUP
        - DSM-5 moderate-to-severe OUD
        - Use opioids in past 7 days

    - Not engaged in medication treatment for OUD
- Proportion who received facilitated referral for treatment amongst those who received some form of ED-initiated BUP.
- Fidelity
    - Critical actions completed

Implementation barriers and facilitators, include:

- Stakeholder acceptability over time (key informant interviews, focus groups)
- ED staff, patient, provider, community barriers and facilitators (key informant interviews, focus groups)

8.3 Tertiary and Exploratory Outcomes

In addition to our revised primary means of assessing the programmatic implementation outcome, we will track methods of data capture to allow us to assess several permutations of this outcome (Reach) to: (i) better match the parent study outcome for improved comparison over time across the parent and ancillary studies and (ii) to refine quality measures that provide more reliable, valid, and complete outcome data and that adequately capture the most salient outcomes in a way that is practical for research and clinical performance monitoring. For example, other measures of reach will include permutations of how the numerator or denominator are defined (e.g., excluding referrals; including only patients identified through EMR documentation). Permutations to effectiveness outcomes and analyses will include evaluation of linkage and engagement over different timeframes (e.g., linkage within 72 hours, 14 days, and 30 days; time-to-event analyses), and evaluations including alternative denominators (e.g., including participants who did not receive ED-initiated BUP). Arguments for shorter timelines are for cases in which BUP is not prescribed; arguments for longer timelines include more remote settings with less treatment availability or if extended-release BUP formulations were used.

Because ED-initiated treatment for OUD is in its infancy, it is essential to first evaluate performance using an approach that maximizes validity and reliability and provides more granular level detail to measure and monitor quality at specific points in the process. Further, it permits analyses of how patient-level characteristics influence completion of measures and effectiveness, which is important to ensuring equitable care. The data collected through the clinical trial using labor-intensive methods will provide a resource – gold standard measures – against which we can compare agreement with quality measures using registry, claims, or other data that will become more feasible as the data infrastructure improves. Although we are unaware of any National Quality Forum (NQF)-endorsed measures specific to the initiation of pharmacotherapy for OUD in the ED and linkage to ongoing treatment, there are measures with potential adaptability to be useable for quality measurement (e.g., NQF #2605, which evaluates the percent linked to alcohol/drug services after an alcohol/drug-related ED visit at 7 days and 30 days). We will assess the utility of using administrative databases (pending availability) for pragmatic evaluation of secondary patient-level outcomes and costs over time such as data from EMRs, health services claims, ambulance reports (transports to EDs, overdose events, costs), the PDMP, and the Departments of Health (vital statistics, mortality), Criminal Justice, and Homeless Services. Dr. Hawk and team members' participation in CTN-0081 provides opportunity to leverage learning across studies as we aim to improve the clinical data infrastructure.

9.0 STUDY PROCEDURES

Study procedures are divided into (1) Implementation Facilitation; (2) clinical protocol sustainability; (3) qualitative procedures and (4) research participant procedures.

9.1 Implementation Facilitation (IF)

An IF booster will be delivered to study sites at the end of the IF Period prior to study start (data collection) using the developed IF procedures detailed in CTN-0069/-0079. The purpose of this "IF booster" is to provide final feedback and help sites transition to independence (designate personnel, etc.) and ensure that processes are in place to allow research staff to collect the needed data with minimal influence on clinical activities.

Key goals of IF during this time period are:

1. Fine tune clinical protocols and provide practical advice.
2. Provide final academic detailing to ensure adequate knowledge, skills, and ability to continue the clinical program without study support.
3. Ensure sites are linked to adequate local and national resources for clinical support.
4. Support an internal continuous quality improvement (CQI) and feedback system/performance monitoring.

We will work with local champions to use the feedback and other data elicited during the parent study close-out assessments (surveys, focus groups, and qualitative interviews) to further refine site-specific clinical protocols and implementation-sustainability plans. We will confirm clinical documentation procedures are established to ensure pragmatic data collection and abstraction for clinical performance monitoring and research assessments.

No further study intervention will occur once trial data collection has begun (i.e., during the Post-IF and Maintenance Periods) with the caveat that the ED-initiated BUP clinical program(s) have not failed to be maintained as discussed (see section 5.4).

9.1.1 Elements of Implementation Facilitation

IF will be based on a manualized program developed by Kirchner and colleagues [13] that has had significant impact on implementing healthcare practices in clinical settings. Building on the mixed-methods analysis conducted during the formative evaluation, we will use the Promoting Action on Research Implementation in Health Services (PARiHS) framework to tailor the IF for site-specific needs. The facilitators and barriers identified by administrators, providers, community stakeholders, and patients and will be characterized according to the PARiHS sub-elements of patient and clinical experience (communication, knowledgeable and empathetic providers), receptive context (resources to provide addiction treatments), and culture (value of team-based approach) identified. The individual components of IF are described below.

9.1.1.1 External Facilitator

Study Investigator content experts will work with local champions to facilitate activities designed to promote implementation of the clinical protocol for OUD tailored to the site-specific needs and applied as needed over the course of the study. They will coach and mentor local champions and encourage the exchange of ideas within and among sites.

9.1.1.2 Local Champions

We will work with local champions to help promote and sustain the ED-initiated BUP clinical program. Local champions will participate in in-person orientation and trainings as well as conference calls with external facilitators during which challenges, barriers, facilitators and strategies will be discussed and documented.

9.1.1.3 Academic Detailing

Academic detailing involves trained clinician consultants visiting other clinicians to share unbiased information about patient assessment and treatment with the goal of improving quality of care [13]. All ED and community providers who may be involved in the initiation or continuation of BUP or assisting with the referral process will be offered educational sessions on OUD and BUP training, specifically tailored to each provider's tasks. Data from the formative and ongoing evaluation during CTN 00079 will be used to potentially modify, remove or add strategies to enhance implementation. We will address practical issues such as efficient use of the EMR for prompts, provide tools and web-based resources such as pcssmat.org and the NIDA and Yale websites on initiating buprenorphine in the ED. Training strategies will be based on adult learning theory and include interactive didactic presentations on the effectiveness and safety of prescribing BUP and skills-based practice sessions, including techniques to enhance motivation. We will offer opportunities and facilitate completing the DATA 2000 waiver for BUP prescribing (currently, free of charge in New York and New Hampshire).

9.1.2 Advising on ED-Initiated BUP Clinical (Non-Research) Sustainability

Serving in an advisory and consultant capacity, we will work with the clinical sites to help them refine previously developed clinical protocols for ED-initiated BUP with facilitated referral. While informed and supported by research, these are clinical guidelines, the contents of which and adherence to, will not be governed by this research. The induction and stabilization guidelines contain a checklist of critical actions similar to those previously tested by D'Onofrio et al.[3] We will provide ongoing consultation to help monitor, support, and refine implementation during the IF activities/booster prior to the start of data collection and enrollment. Adherence to the clinical protocol and, specifically the critical actions related to BUP induction, will be measured by the Clinical Protocol Adherence Log (see section 9.2.2).

9.1.3 Performance Monitoring and Feedback

We will work with ED leaders and other members of the ED staff to incorporate clinician performance related to BUP-initiation and facilitated referral into the department's standard continuous quality improvement (CQI) and feedback practices. Once local CQI methods are established, sites will share CQI data with investigators as available.

9.1.4 Learning Collaborative

Building upon the success of the previous learning collaborative calls for CTN-0079, a Learning Collaborative will be formed during the IF booster month with sites' local champions, and other key stakeholders, to participate in conference calls and or in-person meetings to promote shared learning regarding issues promoting and hindering implementation of addiction treatment. It will provide a dedicated time to discuss site-specific updates, case studies and clinical management, challenges and possible solutions for implementation of ED-initiated buprenorphine with referral to treatment services. Detailed notes will be maintained; this information will be integrated into the evaluation and used to identify site needs that could benefit from targeted IF during this month.

9.2 Clinical Protocol Sustainability

9.2.1 Clinical Protocol Development and Introduction

Clinical protocols, specific to each site were developed, approved, implemented, and continued to be iteratively refined at each site during the parent study. Clinical protocols address screening, assessment, BUP eligibility determination, treatment and referral.

9.2.2 Data Collection on Clinical Protocol Adoption

Qualitative data on clinical protocol sustainability will be via the IF process and qualitative focus groups and interviews at study close. Quantitative data on the impact of clinical protocol implementation will be collected from the EMR and administrative datasets. As in CTN-0079, we will request a full waiver of consent to review data for all patients presenting to the ED at each study site during the study timeline. Research staff will further review the individual charts of those patients screening positive for opioid use to abstract data on fidelity to the clinical protocol. These data will address clinical protocol adherence and impact and support both overall study goals. This dataset will provide the study primary implementation outcome, (i.e., the proportion of patients who receive ED-initiated BUP amongst patients who have been determined to be candidates for ED-initiated BUP).

9.2.3 Clinical Protocol Adherence Log

The Clinical Protocol Adherence Log provides documentation of critical actions (and non-critical actions of interest) for ED-initiated BUP including, but not limited to:

- Meeting criteria for DSM-5 moderate-to-severe OUD confirmed
- Opioid use within 7 days confirmed (by urine toxicology testing or other clinical assessment)
- Assessment of opioid withdrawal conducted (e.g., Clinical Opioid Withdrawal Scale (COWS) score)
- hcG obtained
- ED-initiated/expedited BUP provided
- BUP education and induction instructions provided
- Referral for treatment for OUD provided

Patients will be identified as unique or repeat patients. Basic demographic information (race, ethnicity, sex, age, insurance, etc.) will also be collected. Data are acquired at the patient level for this form to allow for QA of abstraction. All data will be de-identified when entered in Advantage eClinical.

9.3 Qualitative Procedures

At each of the study sites, we will conduct focus groups and/or individual qualitative interviews with a purposive sample of key stakeholders near the close of the study. Purposive sampling is a well-established method in qualitative studies and is designed to identify study participants who have direct experience with or knowledge of the phenomenon of interest, in this case OUDs and ED-initiation of BUP with referral for treatment. We have chosen to use focus groups given their suitability for generating data from multiple perspectives regarding the organizational and individual level factors impacting complex processes when available, and will use one-on-one

semi-structured qualitative interviews for information gathering to allow for the broadest inclusion of perspectives when it is neither feasible nor practical to arrange a suitable focus group [14].

9.3.1 Focus Groups and Qualitative Interviews

We will enroll multiple stakeholders, including but not limited to: ED patients, nurses, social workers, physicians, NPs, PAs, pharmacists, physician and nursing directors at each ED site. In addition, key stakeholders with knowledge or insight into the community-wide impact relating to CTN-0079 will be invited to participate in focus groups and qualitative interviews near study close. A subset of key stakeholders at each site may also be invited to participate in a focus group and/or interview to collect interim information if sustainability fails at the site, as defined in section 5.5.

For staff, we will primarily use focus groups given their suitability for generating data from multiple perspectives regarding the organizational and individual level factors impacting complex processes whereby the group interaction is anticipated to stimulate unique ideas [14]. Focus groups will be conducted with approximately 4-8 study participants each [15].

9.3.2 Development of Focus Group and Interview Guides

The focus group guides will be informed by the PARiHS framework and include “grand tour” questions designed to establish rapport and elicit open-ended responses. Probes will be used to understand specific details of those experiences and allow for clarification of ideas.

9.3.3 Conduct of Focus Groups/Interviews

Focus groups and qualitative interviews will be conducted by Dr. Kathryn Hawk and/or other adequately trained study personnel. All interviews will be audio recorded with the knowledge and permission of the participants.

9.3.4 Informed Consent Procedures

Potential participants recruited for interviews and focus groups will meet with research staff to review all significant elements of the study via an IRB approved verbal script, and the potential participant will be given an opportunity to ask any questions. Following this discussion, and prior to collection of any study-related information, verbal consent to participate in the study will be obtained by research staff. Taking part in the focus group and/or interview is the individual’s agreement to participate, including for audiotaping.

We will work with the EDs and community treatment programs to provide staff assurances that their participation in the research will in no way affect their employment status either positively or negatively. Participants participating in focus groups and qualitative interviews will be reminded that these sessions will involve discussion of sensitive topics, including information regarding health status, opioid use and substance use treatment. Focus groups and interviews will be voluntary and information collected for research purposes will not become part of staff’s personnel records or patients’ medical records.

There is no written (signed) authorization form for focus group participants; a Waiver of Documentation of Consent will be secured, as was done in the parent study.

Individuals who refuse to participate or who withdraw from the study will be treated without prejudice.

9.3.5 Qualitative Data Security and Storage

All qualitative assessments and product will be stored on a password protected, encrypted university owned and secured computer. Audio recordings will be obtained using an encrypted recorder and transcribed by a professional HIPAA-compliant transcription service. Digital audio recordings of interviews and focus groups will be transferred as soon as possible after the recording was made, from the audio recorder to a password-protected secure storage drive. To maximize confidentiality and minimize opportunity of inadvertent voice recognition, audio recordings and unprocessed or unanalyzed transcripts will be accessible only to members of the research team and will not be shared with local site staff, administrators or local champions. All hard copies of data will be maintained in a secure locked cabinet, accessible only to research staff. Recordings on the recorder will be destroyed following their transcription, and recordings on the secured storage drive will be maintained until the transcripts are reviewed in their entirety and no questions related to inaudible or inaccurately transcribed portions remain. These recordings will subsequently be destroyed.

9.3.6 Qualitative Participant Incentives

Patients and providers will receive a $25 incentive for participating in a focus group or a one-on-one qualitative interview. See section 12.13 for Qualitative Statistical Analyses.

9.4 Research Participant Procedures

9.4.1 Full Study Participants

Patients who are determined to meet Full Study eligibility criteria (section 7.2) will be invited to participate in the Full Study, which consists of two research visits and providing authorization for research staff to access their health records and to link/match their Protected Health Information (PHI) and Personally Identifiable Information (PII) to administrative data (e.g., PDMP, claims) for a period beginning 1 year prior to study enrollment through 2 years following study enrollment. As described in the Manual of Operations (MOP), the baseline research visit will ideally occur at the index ED visit or within 72 hours of ED discharge, but recruitment efforts may continue for up to 7 days post discharge. The Day 30 follow-up visit (30 days post ED discharge) will ideally occur no more than 7 days after this target, although outreach to reengage participants lost to contact may continue past this point.

9.4.1.1 Recruitment

Research staff will work rotating shifts in the ED, providing coverage on weekdays, evenings, and weekends. Shifts will be scheduled so that patients can be recruited on all days of the week. During recruitment shifts, research staff will approach ED patients in a prioritized order, such that patients who are most likely to be eligible will be approached first. For example, patients who present to the ED seeking treatment for OUD or who were identified through triage screening to have non-medical opioid use would be approached before other patients; prioritization procedures will be further described in the MOP. The integration of opioid screening into clinical care via CTN-0079 will facilitate pragmatic identification of potential participants.

Research staff will screen and assess ED patients for study eligibility using questions embedded in a health survey (ED Health Survey). We have successfully used the strategy of embedding substance use questions in a general health survey as a method to screen for drug and alcohol use.[16, 17] Embedded questions have also been noted by the World Health Organization to improve the reliability of self-reported behavior.

Upon approach, the RA will use an IRB-approved script to seek permission to complete the ED Health Survey. A Waiver of Documentation of Informed Consent will be requested to complete the ED Health Survey. The ED Health Survey will begin with introductory questions (e.g., patients' access to a primary care provider and transportation) followed by use of legal substances (tobacco, alcohol) prior to asking about opioid use. Patients endorsing non-medical opioid use will then be asked to provide verbal consent to answering a series of simple questions to assess whether they are likely candidates for ED-initiated BUP, including the DSM-5 checklist for OUD (see section 7.2) and, if so, additional questions to determine eligibility for study participation (e.g., prisoner status assessment).

Patients who receive ED-initiated BUP during times without research staff coverage will be contacted for potential study participation as soon as possible following ED discharge. Candidates who do not receive BUP will not be contacted once they have left hospital premises. As in the parent study, research staff will utilize available contact information, including information provided at registration or documented in the EMR, to contact candidates, assess eligibility, and offer study participation. Each site's clinical protocol includes a procedure to notify ED patients that clinical or research staff may contact them for follow up purposes and/or to discuss participation in a research study. Patients may opt out of contact from research staff. Assessment of study eligibility will be conducted by trained research staff and may be completed by phone or in person (upon return). Candidates who are determined to be eligible for and interested in study participation will be scheduled for written consent and baseline assessments to be completed in person, ideally within 72 hours of ED discharge but recruitment efforts may continue for up to 7 days post ED discharge.

It is anticipated that some patients will be difficult to reach due to insufficient contact information, homelessness, admission to a treatment program, or other reasons. Of the patients reached, it is expected that some may choose not to participate and that some patients may fail to present for the baseline visit within the visit window. Research staff will make repeated attempts (at varying times of the day- morning, afternoon, evening) to contact all candidates utilizing multiple methods of communication (i.e., call, text, email). Research staff will also strive to reduce barriers to participation by offering to complete the visit at a time and location that is convenient for the participant. All candidates will be informed that they will receive compensation for participation.

We will strive to keep recruitment relatively even across all sites through purposive sampling and employing a recruitment strategy, defined in the MOP, that includes enrollment rate limits based on the relative number of participants enrolled at each site. As our effectiveness outcomes focus primarily on recipients of ED-initiated BUP, we will also employ a recruitment strategy that preferentially enrolls patients receiving ED-initiated BUP to those not receiving ED-initiated BUP. Similarly, we will preferentially enroll females as they are known to be underrepresented.

9.4.1.2 Informed Consent

Patients endorsing non-medical opioid use on the ED Health Survey and who are not currently taking prescription opioids or MOUD, will be asked to provide verbal consent to complete screening procedures. After the individual has provided verbal (not signed) consent, research staff will complete the DSM-5 checklist for OUD, demographic information, and confirm that the candidate meets all the inclusion criteria and none of the exclusion criteria. Candidates who meet all eligibility criteria will be offered participation. Reasons for exclusion or non-participation will be documented. Candidates who do not meet eligibility for the Full Study, will be assessed for participation in the Limited Study (section 10.15).

All candidates remaining eligible following this study screening will be asked to provide written informed consent to participate in both data matching and research assessments using the IRB-approved informed consent document. Prior to documenting written informed consent, research staff will explain the study to the potential participant and provide a copy of the consent to read and reference during the consent discussion. All candidates 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. A discussion of risks and possible benefits will take place with the participants. Candidates will have the opportunity to carefully review the written consent form and ask questions prior to signing. If the candidate is interested in participating in the study, a research staff member will review each section of the IRB-approved informed consent form in detail and answer any questions the participant may pose.

We will seek approval from the IRB of record to use of a compound authorization form that serves as a combined consent and HIPAA disclosure form allowing study access to PHI and PII in the participant's health record.

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.

Future research: We will seek permission to contact the participant in the future about other research opportunities; however, permission for future contact is not required for participation.

The candidate will consent by signing and dating the consent document. The person obtaining consent will also sign and date the consent document. The participant should be given a copy of the signed consent to keep for their records. Study sites will be responsible for maintaining original signed consent forms as source documents for quality assurance review and regulatory compliance.

9.4.1.3 Eligibility Confirmation and Enrollment

Once eligibility is confirmed, and all consents are fully executed, the candidate will be considered enrolled in the study. The enrollment procedures will be captured through a centralized process managed by the CTN Data and Statistics Center (DSC). Patients who do not complete screening or who are otherwise found to be ineligible for participation in the Full Study will be considered screen failures. These individuals who fail screening or refuse Full Study participation, may be assessed for Limited Study participation (section 10.15).

9.4.1.4 Baseline Procedures

Baseline procedures will continue with structured assessments on quality of life, substance use, and healthcare utilization. See Table 3 for a complete list of study assessments. Baseline procedures will ideally be completed at or within 72 hours of ED discharge by research staff via medical records abstraction and interview with study participants.

9.4.1.5 Intervention

All patients who screen positive for non-medical opioid use will receive an informational pamphlet related to OUD treatment and harm reduction.

9.4.1.6 Follow-up Visit (Day 30)

The follow-up research visit will assess engagement in treatment on the 30th day after discharge from the index ED visit. At the follow-up visit, participants will be asked to provide a urine sample and complete specified research assessments (see Table 3: Schedule of Assessments).

9.4.1.7 Participant Retention

Rigorous retention strategies will be employed to maintain contact with participants throughout the duration of the study and to minimize missing data. Broadly, retention methods may include outreach to the participant and their identified contacts through mailed letters, email reminders, phone calls, text messaging, social media, in-person contact, and/or public database searches. All tracking and retention materials will be IRB-approved.

9.4.1.8 Premature Participant Withdrawal

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, clinical documentation post enrollment that the patient is not a candidate for ED-initiated BUP, the participant becoming a threat to self or others, lack of funding, or DSMB early termination of the study for safety or effectiveness reasons.

9.4.1.9 Participant Reimbursement

Participants will be compensated for their participation in the Full Study. Each will receive $75 for completion of screening and baseline assessments and $100 for the Day 30 follow-up visit.

9.4.2 Limited Study Participants

ED patients who do not meet Full Study eligibility criteria or who refuse Full Study participation may be eligible to participate in the Limited Study. Limited Study participants will be identified through the same recruitment process as Full Study participants; however, once candidates screen out for the Full Study (see sections 7.2 and 7.3), they will continue to be assessed for possible Limited Study participation. Limited Study participation will only be offered to those candidates who complete screening in person (i.e., patients who are no longer in the hospital will only be offered participation in the Full Study if they are eligible). Once all inclusion criteria and none of the exclusion criteria have been met, the candidate will be presented with an Information Sheet outlining the purpose of the Limited Study, information to be accessed, and how the information will be used. If the patient remains interested in participating, the patient will be asked to certify they have read and understand the study procedures, as well as, provide consent authorizing release of medical information and use of PHI and PII so that we may link their survey and other research data with administrative databases. The authorization period will be valid for two years from the date of signing (i.e., study enrollment) and one year retrospectively (candidates will have the ability to opt out of releasing retrospective data one year prior to study enrollment). The candidate will be provided sufficient time to read through both the medical release and information sheet and will receive a verbal explanation of study procedures suited to their comprehension level. Candidates will be given time to ask questions before signing the medical release and information sheet. Limited Study participants will receive a pamphlet on OUD and receive $25 compensation for their time completing in person assessments. Limited Study participants will be enrolled into the project through a centralized process managed by the CTN Data and Statistics Center (DSC). Once the participant has completed screening and is enrolled into the Limited Study, all remaining assessments will be completed via chart review or available data and without participant input. See Table 3: Schedule of Research Assessments – Full and Limited Study. The data for these assessments will be abstracted via manual searches from

EMRs and databases (e.g., PDMP) according to procedures established in the parent study. We will also link Limited Study participants' PHI and/or PII to administrative data for the purposes of data matching, pending availability (Data Use Agreements) as will be done with the Full Study population and all adult ED patients screening positive for non-medical opioid use, via a Waiver of Consent.

10.0 RESEARCH ASSESSMENTS

10.1 Table 3: Schedule of Research Assessments – Full and Limited Study

	All	Full Study		Limited Study
Assessment*	**Screening & Enrollment**	**Baseline**	**Day 30**	**Day 30**
ELIGIBILITY				
Introductory Script/Permission for ED Health Survey	X			
ED Health Survey	X			
Verbal Consent	X			
DSM-5	X			
Additional Demographics	X			
Prisoner Status Assessment	X			
Patient Eligibility	X			
Enrollment (Inclusion/Exclusion)	X			
Written Informed Consent (i.e., compound authorization form) (Full Study only)	X			
Information Sheet (with authorization)(Limited Study only)	X			
Medical Releases	X			
GENERAL				
Demographics	X			
Locator Information Form		X	X	
Other Substance Use		X		
PROMIS-29		X	X	
Motivations, Attitudes and Expectations		X		
Study Completion			X	X
HEALTH SERVICES				
Inpatient Utilization		X	X	
Outpatient Utilization		X	X	
Health Status		X	X	
Healthcare Visit Logistics		X		
ED Visit Review		X		X**
ED Visits and Hospitalizations			X	X
PROCESS OUTCOMES				
Engagement in Treatment - Patient			X	
Engagement in Treatment - Facility			X	X
Prescription Drug Monitoring			X	X
Treatment Satisfaction/Acceptability			X	
Treatment Effectiveness Assessment (TEA)		X	X	
OPIOID OUTCOMES				
Timeline Follow-Back (TLFB)		X	X	
Urine Drug Screen		X	X	
Overdose Events & Risk Factors		X	X	
SAFETY				
Safety Events		X	X	X
Mental Health Assessment+		X	X	

** All participant-facing documents will be reviewed/approved by the IRB. Minor edits may be made to assessments (e.g., grammar, punctuation, directions, system programming, etc.) as needed. Assessments will only be submitted for re-review if information to be collected is changed (e.g., addition of new questions.).*
***To be completed after enrollment and prior to Day 30 for Limited Study participants*
+As triggered by participant responses on the HST form.

10.2 Eligibility

ED Health Survey: This assessment will be conducted with patient permission through a Waiver of Documentation of Informed Consent. It will include questions about illicit opioid use embedded in a general health and substance use screener that also includes questions about tobacco and alcohol use. This form will be completed via self-report and potentially supplemented via medical record abstraction (e.g., rather than re-asking data collected clinically, the RA may review data with the patient to ensure accuracy and minimize patient frustration associated with redundancy) for all study candidates.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5): The DSM-5 criteria are assessed during screening to determine a current diagnosis of moderate-to-severe opioid use disorder. This assessment will be completed electronically in eClinical and will be automatically scored.

Additional Demographics: The additional demographics form collects information on health insurance, income, employment patterns, and housing information. This form is completed once at screening for all study candidates.

Prisoner Status Assessment: The Prisoner Status Assessment is a brief form collecting information related to current detainment, house arrest and/or probation status to determine whether the candidate meets the definition of a prisoner as delineated in 45 CFR 46.303(c) at the time of the index ED visit. This form will be completed once at screening for both Full and Limited Study participants. Candidates meeting prisoner status at screening will not be enrolled in either the Full or Limited study.

Eligibility Measures: These forms collect information regarding study eligibility. The Patient Eligibility form documents eligibility criteria collected during screening. Prior to informed consent, the inclusion and exclusion criteria are assessed and documented on the Inclusion/Exclusion Checklist and Enrollment form. Only individuals who continue to meet study eligibility criteria are allowed to continue with the screening process, and enrollment. Both limited and Full Study participants will complete eligibility assessments.

10.3 General

Demographics: The demographics form collects information about demographic characteristics of the study candidate, including date of birth, sex, racial/ethnic group, educational level, marital status, and employment status. The demographics form will be completed once at enrollment for both Full and Limited Study participants.

Locator Information Form: A locator form is used to obtain information to assist in finding patient-participants during follow-up. 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, as well as information such as social security number, driver's license number and other information to aid in searches of public records. Two valid contacts are required for study eligibility. This information will be collected at baseline and updated at the Day 30 follow-

up for Full Study participants only. Data entered in this form will be encrypted and will not be used in data analyses.

Other Substance Use: Selected questions from the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)-lite [18] will be used to assess drug and alcohol use over the past 3 months and will be asked at baseline for Full Study participants only.

PROMIS-29: Health-related quality of life (HRQoL) will be measured using the Patient-Reported Outcomes Measurement Information System (PROMIS).[19, 20] PROMIS was developed using item response theory, with support from the NIH. Because of its foundation, PROMIS is able to improve upon common deficiencies of existing, widely-used, HRQoL instruments capable of generating a single health utility index value for the calculation of QALYs [21-24] including: floor and ceiling effects among participants who are especially ill or healthy, respectively, and imprecise questions that blend concepts.[25] The PROMIS-Preference (PROPr) scoring system uses the respondent's scores for each of the following PROMIS domains to calculate a health utility index value that represents the general US population's preference for the respondent's current health state: Cognitive Function–Abilities, Depression, Fatigue, Pain Interference, Physical Function, Sleep Disturbance, and Ability to Participate in Social Roles and Activities.[26, 27] PROMIS has 5 levels for each domain: no problems, slight problems, moderate problems, severe problems, and extreme problems. The health-utility value produced by PROPr can range from -0.022 to 1, where 0 represents death, 1 represents perfect health, and values below 0 represent states perceived to be worse than death. Construct validity for PROPr has been demonstrated using other HRQoL instruments and two large datasets from the general US population.[25] The health-utility value is then used to calculate QALYs, as our team, and many others have done in similar studies.

Motivations, Attitudes and Expectations: Motivation for participating in the study and attitudes and expectations regarding medication treatment for OUD are collected once at baseline for Full Study participants.

Study Completion: This form tracks the participant's status in the study through the Day 30 visit. It is completed for both Full and Limited Study participants after completion of the Day 30 follow-up or once the visit window lapses for participants who do not complete the Day 30 follow-up. This form is used in data analyses to address variables such as treatment retention and completion. This form also provides a location for the site PI attestation of review of all study data entered in eClinical.

10.4 Health Services

Health Services Utilization Inpatient and Health Services Utilization Outpatient: A brief, structured interview regarding health care utilization (inpatient and outpatient) will be used, which collects information on the type and amount of services received. This includes ED visits, hospitalizations, primary medical care visits (excluding those for buprenorphine treatment and 12-step group sources of support (e.g., Narcotics Anonymous). It is completed at baseline and at the Day 30 follow-up visit for Full Study participants only.

Healthcare Visit Logistics: The Healthcare Visit Logistics form collects information on distance to healthcare providers (e.g., how many miles patient-participants drive to providers). This form is completed once at baseline for Full Study participants.

Health Status: The Health Status form collects information on HIV and Hepatitis C status, pain (PEG), and psychological health (PHQ-9), usual care and reason for the ED visit. Health status

questions are collected at baseline and the Day 30 follow-up visit for Full Study participants. The Mental Health Assessment form is triggered if the participant responds that they have had "Thoughts that you would be better off dead, or of hurting yourself in some way" over the past two weeks in the PHQ-9 section of the form.

ED Visit Review: The ED Visit Review form collects information about the index ED visit including enrollment date, discharge date and time, chief complaint, critical actions completed, and discharge diagnosis. It is completed by research staff via medical chart review and without participant input for both limited and Full Study participants.

ED Visits and Hospitalizations: The ED Visits and Hospitalizations form collects information about the index ED visit and any visits or hospitalizations at the site between the index visit and follow-up. It is completed at the Day 30 follow-up visit. Data are gathered by research staff via medical chart review and without participant input for both Limited and Full Study participants.

10.5 Process Outcomes

Engagement in Treatment Survey: At the Day 30 follow-up visit Full Study participants will be asked to report whether they are engaged in formal addiction treatment. Data will be reported on the Engagement in Treatment: Patient survey. The outcome will be confirmed with the addiction treatment provider using the Engagement in Treatment: Facility survey, which includes the type of treatment the participant is receiving, i.e., methadone, buprenorphine and/or naltrexone treatment, detoxification, inpatient or outpatient treatment. Date of admission is recorded as well as the level of treatment received according to ASAM Levels of care, such as Level I: Outpatient Treatment; Level II: Intensive outpatient treatment (including partial hospitalization); Level III: Clinically managed residential/inpatient treatment; Level IV: Medically managed intensive inpatient treatment or Other-specified. Engagement in Treatment: Facility survey will be completed with both Full and Limited Study participants. ED visit is considered Day 0; Engagement is assessed on Day 30.

Prescription Drug Monitoring: The states' Prescription Drug Monitoring Programs will be accessed to identify all opioid prescriptions that participants fill during the follow-up period (date of ED discharge through Day 30). This form will be completed once at the Day 30 visit for both Full and Limited Study participants. This form is completed via database review and without participant input.

Treatment Satisfaction/Acceptability: This form will be completed at the Day 30 follow-up visit for Full Study participants. This form will collect information on satisfaction with and acceptability of OUD treatment received throughout the study.

Treatment Effectiveness Assessment: This form will be completed at the baseline and Day 30 follow-up visit for Full Study participants. This form collects self-report data across four domains: substance use, health, lifestyle, and community.

10.6 Opioid Outcomes

Timeline Follow-Back (TLFB): The Timeline Follow-Back[28] procedure will be used to elicit the Full Study participant's self-reported use of illicit substances at baseline and throughout study participation. The TLFB will be administered at baseline for the 7-day period prior to the index ED visit. At the Day 30 follow-up visit the assessment period will be the 7 days preceding the Day 30 post index ED visit.

Overdose Events and Risk Factors: We will ask Full Study participants about opioid-related overdose events, overdose prevention, and overdose risk factors. This form will be completed at baseline and at the Day-30 follow-up visit for Full Study participants only.

Urine Drug Screen: Urine testing will be performed for the presence of the following drugs: opioids, oxycodone, PCP, benzodiazepines, cocaine, methamphetamine, amphetamine, 3.4-methylenedioxy-methamphetamine (MDMA), tetrahydrocannabinol (THC), barbiturate, methadone, fentanyl, and buprenorphine. The urine drug screen is conducted by research staff for research purposes only. UDS results will not be entered into the medical chart. The UDS is performed at baseline and the Day 30 follow-up visit for Full Study participants. Urine testing supplies will be provided to the sites.

Overdose Events and Risk Factors: The Overdose Events and Risk Factors form is completed at baseline and Day 30 for Full Study participants. This self-report form collects information on overdose risk, experience with Naloxone, and past 30-day opioid overdose events.

10.7 Safety

Mental Health Assessment: The Health Status form contains a question that asks participants if they have had "thoughts that you would be better off dead, or of hurting yourself in some way" over the past two weeks. For "in-person" research visits (i.e., either on site or in the field where clinician assessment resources are reasonably available), any response other than "Not at all," will prompt a clinician assessment for suicide risk and trigger a requirement for the completion of the "in-person" version of the Mental Health Assessment form by the RA. The Mental Health Assessment form documents the performance of the required direct clinician evaluation of the participant for suicide/homicide risk according to the site-specific SOP. This clinician evaluation should take place prior to the participant leaving the study site. A protocol deviation is required if the clinician evaluation is not completed prior to the participant leaving the study site for in person research visits. For participant research visits *not* conducted in person or in a location that is physically remote from reasonably available clinician assessment resources, the "remotely" version of the Mental Health Assessment form should be completed to document provision of national or local mental health resource referral/contact information to the participant. A protocol deviation is required if these referral/contact information resources are not provided to the participant prior to the participant leaving the remote visit site. The Mental Health Assessment form is not completed when suicidality/homicidality is not endorsed on the respective Health Status form question (e.g. spontaneously reported by a participant). In these cases, the assessment of reported suicidality/homicidality will be conducted in accordance with the study site's standard of care procedures. Consequently, all sites should monitor participant responses to the Health Status form, as well as spontaneous expression of potential participant suicidal/homicidal ideation, and have procedures in place to ensure participant safety.

Opioid non-fatal overdose events, healthcare utilization including ED visits and hospitalizations, suicidal ideation, and all deaths including fatal overdoses will be tracked beginning at the time of consent and ending with participant study completion at the Day 30 visit. Overdose events since enrollment will be captured by participant self-report, potentially collateral report (e.g., family), review of health records and EMS records (pending availability). In the event of Full Study participant withdrawal/loss to follow-up and in the case of all Limited Study participants, we will attempt to track fatal overdose events and other mortality through Offices of Vital Statistics, Offices of the Certified Medical Examiner, and/or local morgues. Overdose events will be recorded on the Overdose Events and Risk Factors form. Research staff may become aware of safety events in between study visits (i.e., via participant family and friends, ED visits, etc.). These non-fatal events should be recorded on a study progress note to prompt data entry of the event at the

next research visit. Deaths will be entered into the database in real time, as staff become aware of the event. Since BUP is provided consistent with community practice, a medication adverse event profile will not be maintained. Each facility has SOPs to address safety events including overdose and suicidality and other psychiatric emergencies, and these will be followed. When a medical or psychiatric emergency is identified, including presence of potential suicidal ideation, research staff will activate local procedures to ensure participant safety. As there is no planned interaction between Limited Study participants and research staff post enrollment, research staff will not actively intervene when safety events are identified in Limited Study participants.

11.0 RESEARCH STAFF TRAINING

Research staff will be trained as specified in the Study Training Plan developed by the Lead Node, the CCC, the DSC, and other members of the Lead Team. Additional details and guidance for study procedures will be provided in a Manual of Operating Procedures (MOP) and in local SOPs. Research staff training will be conducted via in-person training sessions, webinar presentations, and/or telephone conferences. Required training will include Human Subjects Protection (HSP) and Good Clinical Practice (GCP), as well as protocol-specific training as needed (e.g., assessments, safety procedures, data management and collection). Research staff collecting and entering data in Advantage eClinical will complete training on electronic case report form (eCRF) data entry, data management and integrity, and the Advantage eClinical data system. In-person practicums will be required of study staff conducting the recruitment, Informed Consent, urine drug screening, and the TLFB. All study staff will be required to complete the study-specific training plan for their assigned study role as well as satisfy any training requirements per local institutions.

12.0 STATISTICAL DESIGN AND ANALYSES

12.1 General Design

CTN-0079-A1 is an implementation study that will use mixed methods and triangulate multiple sources of data collected over the course of the parent (CTN-0079) and the ancillary studies to evaluate the feasibility, acceptability, sustainability, and impact of the ED-initiated BUP clinical program and implementation facilitation strategy and identify factors influencing diffusion and effectiveness. The ancillary study involves three phases of participation: 1) candidates for ED-initiated BUP enrolled over a 12-month period (Post-IF and Maintenance periods, 6 months each) to participate in two research visits (Days 0 and 30) and/or authorize administrative data matching, 2) ED staff, patients, and stakeholders' participating in semi-structured qualitative interviews/focus groups at study close, and 3) retrospective chart review and data matching for all adult ED patients identified to have non-medical opioid use presenting to the ED during the IF, Post-IF or Maintenance periods.

12.2 Recruitment and Enrollment

The ancillary study participants are planned to be identified from parent study sites: Catholic Medical Center, Valley Regional Hospital, and Bellevue/NYC Health and Hospitals. The study population will consist of ED patients who are candidates for ED-initiated BUP. We anticipate that, 300 ED patients (150 identified during each ancillary study period) will be found that meet this criterion. This is the population for evaluating the primary and key secondary implementation outcomes. Of those patients, approximately 120 (i.e., 120/300=40%, with 60 participants enrolled during each ancillary study period) will enroll as Full Study patient-participants. This is the population for evaluating the primary and key secondary effectiveness outcomes. We also anticipate that as many as an additional 180 patient-participants will enroll in the Limited Study and have included an additional 20 Limited Study patient-participants in case this number is higher than anticipated for a total N=300 (120 + 180 + 20) for data matching outcomes. Based on data from parent study, we approximate 40% to 90% of ED patients that are eligible for and willing to receive ED-initiated BUP will actually receive it, and 40% to 80% of enrolled patient participants will be engaged in formal treatment within 30 days following ED discharge. Table 4 shows the expected cumulative number of individuals identified and those anticipated to receive ED-initiated/expedited BUP for primary implementation outcome, as well as the number of individuals enrolled and engaged in formal treatment for primary effectiveness outcome. We present the number of expected ED-initiated/expedited BUP receivers and those engaged to formal treatment for the lowest and highest success rates (i.e., 40% and 90% for primary implementation outcome, and 40% and 80% for primary effectiveness outcome).

z	Phase	Primary Implementation Outcome N=300			Primary Effectiveness Outcome N=120		
		Number identified	Number who received ED-initiated/expedited BUP assuming, 40% - 90% success rates		Number enrolled	Number engaged in formal addiction treatment for OUD, assuming 40% - 80% success rates	
			40%	90%		40%	80%
	Post-IF Period						
1		25	10	23	10	4	8
2		50	20	45	20	8	16
3		75	30	68	30	12	24
4		100	40	90	40	16	32
5		125	50	113	50	20	40
6		150	60	135	60	24	48
	Maintenance Period						
1		175	70	158	70	28	56
2		200	80	180	80	32	64
3		225	90	203	90	36	72
4		250	100	225	100	40	80
5		275	110	248	110	44	88
6		300	120	270	120	48	96

Table 4: Expected cumulative numbers of individuals capable of being assessed for selected study milestones outcomes across Post-IF and Maintenance Periods by month

12.3 Primary and Secondary Outcomes Measures

12.3.1 Definition of Primary Implementation Outcome

The primary implementation outcome measure is receipt of ED-initiated/expedited BUP. This is a binary outcome and will be defined as the proportion of ED patients receiving ED-initiated/expedited BUP amongst ED patients who are candidates for ED-initiated BUP. Receipt of ED-initiated/expedited BUP will be operationally defined to include: (1) administration of BUP in the ED, (2) prescription for BUP as part of the ED visit, or (3) provision of a specific "warm" referral or transfer of care to a provider, clinic, or treatment setting with the capacity to administer or prescribe BUP within no more than 24 hours. Data for implementation primary outcome will be abstracted from the health record (EMR abstraction) and/or determined through research staff assessments. The outcome will be calculated as a pooled success rate over Post-IF and Maintenance periods.

12.3.2 Definition of Primary Effectiveness Outcome

The primary effectiveness outcome measure is engagement in formal addiction treatment for OUD on the 30th day following ED discharge. The primary effectiveness outcome is defined as: the proportion of participants who are confirmed to be engaged in formal addiction treatment for OUD on the 30th day following ED discharge, amongst participants who received ED-initiated/expedited BUP. The outcome will be calculated as a pooled success rate over Post-IF and Maintenance periods.

12.3.3 Secondary Outcomes Measures

12.3.3.1 Secondary Implementation Outcome Measures

The key secondary implementation outcome measure is receipt of ED-initiated BUP. This is a binary outcome and will be defined as the proportion of ED patients receiving ED-initiated BUP amongst ED patients who are candidates for ED-initiated BUP. The outcome will be calculated as a pooled success rate over Post-IF and Maintenance periods.

Other secondary Implementation outcomes will include other measures of reach, including evaluating ED-initiated BUP as a function of time. That is, evaluating the rate of ED-initiated/expedited BUP provided via the ED over the course of the CTN-0079-A1 study with rates of ED-initiated BUP provision estimated secondarily. The outcome measures are: (i) rates of BUP provision between the Post-IF and Maintenance Periods and (ii) diffusion curves in which the number of patients provided BUP is displayed graphically as a function of time.

Other RE-AIM model dimensions to be assessed include: provider adoption measured by the number and proportion of ED providers who have (i) provided BUP treatment and (ii) completed DATA 2000 training to become a BUP prescriber, and Implementation fidelity (proportions for adherence to clinical actions associated with the delivery of ED-initiated BUP). Maintenance will be assessed by evaluating these patient- and setting-level outcomes ≥ 6 months after the cessation of all study-supported IF (i.e., the Maintenance Period).

12.3.3.2 Secondary Effectiveness Outcome Measures

The key secondary effectiveness outcome is linkage to formal addiction treatment for OUD within one week (operationalized at within 7-10 days). This is a binary outcome and will be defined as the proportion of participants with (objectively) confirmed linkage to formal addiction treatment for OUD within one week following ED discharge, amongst participants who received ED-initiated/expedited BUP. The outcome will be calculated as a pooled success rate over Post-IF and Maintenance periods.

Other secondary effectiveness analyses will evaluate the participant subgroups who received ED-initiated BUP and ED-expedited BUP separately as well as those who did not receive BUP.

As in the parent study, a range of secondary effectiveness measures will be assessed at the index ED and Day 30 visits, including but not limited to:

- Self-reported days of opioid and other drug use (TLFB)
- UDS results at 30 days post index ED visit
- Overdose events
- Healthcare utilization
- Quality of Life, Health, and Treatment Effectiveness (PROMIS-29, PHQ-9, TEA)
- Treatment satisfaction and acceptability

Process measures related to the clinical protocol include but are not limited to:

- Proportion of ED patients triaged who are screened for non-medical opioid use
- Proportion of those screened who are positive for non-medical opioid use
- Among those positive:

- Proportion who are candidates to receive ED-initiated BUP
- Proportion who receive ED-initiated BUP (and whether via direct administration, prescription, and/or warm referral within 24 hours)
- Numbers meeting inclusion/exclusion criteria for ED-initiated BUP
  - DSM-5 moderate-to-severe OUD
  - Use opioids in past 7 days
  - Not engaged in medication treatment for OUD

- Proportion who received facilitated referral for treatment amongst those who received some form of ED-initiated BUP.
- Fidelity
  - Critical actions completed

Implementation barriers and facilitators, include:

- Stakeholder acceptability over time (key informant interviews, focus groups)
- ED staff, patient, community barriers and facilitators (key informant interviews, focus groups)

12.4 Statistical Methods for Primary Analyses

Primary and key secondary Implementation outcomes analyses will be descriptive in nature, no inferential analysis will be performed. The analyses will examine the overall implementation probabilities (proportions) across the Post-IF and the Maintenance Periods and calculate corresponding 95% confidence intervals. Analyses of the primary and key secondary effectiveness outcomes will follow the approach used for the primary and key secondary implementation outcomes. Each outcome will be presented as an overall effectiveness probability (proportion) across the Post-IF and Maintenance Periods, with a corresponding 95% confidence interval.

12.5 Precision Analyses for Primary Outcomes

We assume that 300 ED patients (150 at each ancillary study period) identified uniformly across the 3 sites will be found to be candidates for ED-initiated BUP. This is the population for the denominator of the primary implementation outcome. We also assume that, of these, approximately 120 participants will get enrolled in the Full Study and become available to evaluate the effectiveness primary outcome. Based on previous assumptions, and data from the parent study, we assume that the true proportion (success rate) of these individuals that actually receive ED-initiated BUP is between 40% to 90%, and the true proportion (success rate) of participants who were engaged in formal addiction treatment for OUD on the 30th day following ED discharge is between 40% to 80%.

12.5.1 Simulation Approach

We investigated the bias and the distribution of the widths of the 95% confidence intervals for the primary implementation outcome measure (i.e., probability of receiving ED-initiated/expedited BUP), and the primary effectiveness outcome measure (i.e., probability of engagement in formal addiction treatment for OUD on the 30th day following ED discharge). The simulations were based on 10,000 iterations assuming the effect of site differences on the outcome measures (site variability) of: $\Delta = (0,0.1,1,2,3)$ and the success rates $(\mathrm{p}) = (0.4,0.5,0.6,0.7,0.8,0.9)$ for the

implementation outcome and the success rates $(\mathrm{p}) = (0.4,0.5,0.6,0.7,0.8)$ for the effectiveness outcome. We investigated the 95% confidence interval widths for N=180, N=240 and N=300 for the primary implementation outcome and N=60, N=90 and N=120 for the primary effectiveness outcome.

Like the parent study, we use Bayesian estimates for the site-level probability value, assuming beta likelihoods uniform priors to derive posterior moments. That is, if there are S successes and F failures for a site across the Post-IF and Maintenance periods, we take the implementation probability estimate for that site to be $\alpha/(\alpha+\beta)$, with estimated variance $\alpha\beta/[(\alpha+\beta)^2(\alpha+\beta+1)]$, where $\alpha = S+1$ and $\beta = F+1$. We take the overall site success rate estimate to be the average of the three site-level estimates. Because the site-level estimates are independent, the variance of the overall estimate is the sum of the site-level variances divided by 9. To construct confidence limits, we assume the overall estimate is roughly normal in distribution, with upper and lower 95% confidence intervals given by $\pm 1.96 * \sqrt{V_{overall}}$. An exception to this is that we did not allow confidence limits to stray outside (0,1). Same simulation approach was used for primary effectiveness outcome precision analyses.

Simulation SAS code

SAS code to perform this calculation is below. We assume the results of the trial are in file SIMUL, where there is one record per patient, with variables Y, site, and phase, where:

- *y* = 1 if the ED-BUP was implemented for this patient, and 0 otherwise
- *site* = 1, 2, or 3, depending on the site of the patient
- *phase* = 1 if the patient was identified during Post-IF period and phase=2 if the patient was identified during the Maintenance period.
- The outcome of the calculations is in file EST, where:
- (*e1, e2, e3*) are the site-specific estimates of the implementation probabilities across Post-IF period and Maintenance period
- (*v1, v2, v3*) are the estimated variances for (*e1, e2, e3*)
- (*pest*) is the estimated implementation probability across Post-IF period and Maintenance period
- (*lclest, uclest*) is the corresponding 2-tailed 95% confidence limit.

```
proc summary nway data = SIMUL;
 class site;
 var y;
 output out = summ sum=;
 run;

data summ;
 set summ;
 heads = y;
 tails = _freq_-y;
 alpha = heads+1;
 beta = tails+1;
 e = alpha / (alpha + beta);
 v = alpha * beta / ((alpha + beta)**2 * (alpha + beta + 1));
 keep heads tails e v;
 run;
```

```
%macro t(what);
 proc transpose data = summ out = tsumm&what prefix = &what;
   var &what;
   run;
 %mend t;

%t(e);
%t(v);

data est;
 merge tsumme tsummv;
 /* intentional merge without BY statement */
 drop _name_;
 pest = (e1 + e2 + e3)/3;
 vest = 1/9 * (v1 + v2 + v3);
 lclest = min (1, max (0, pest - 1.96 * sqrt(vest)));
 uclest = max (0, min (1, pest + 1.96 * sqrt(vest)));
 ciwidth = uclest - lclest;

 run;
```

The same SAS code was used for the primary effectiveness outcome precision analyses.

12.5.2 Simulation Results

Below we present the 90th percentile of the distribution of the 95% confidence interval widths and the bias for the implementation and effectiveness probabilities across Post-IF and Maintenance periods. Figures 2-3 present plots for the implementation probability and 3-4 present plots for the effectiveness probability.

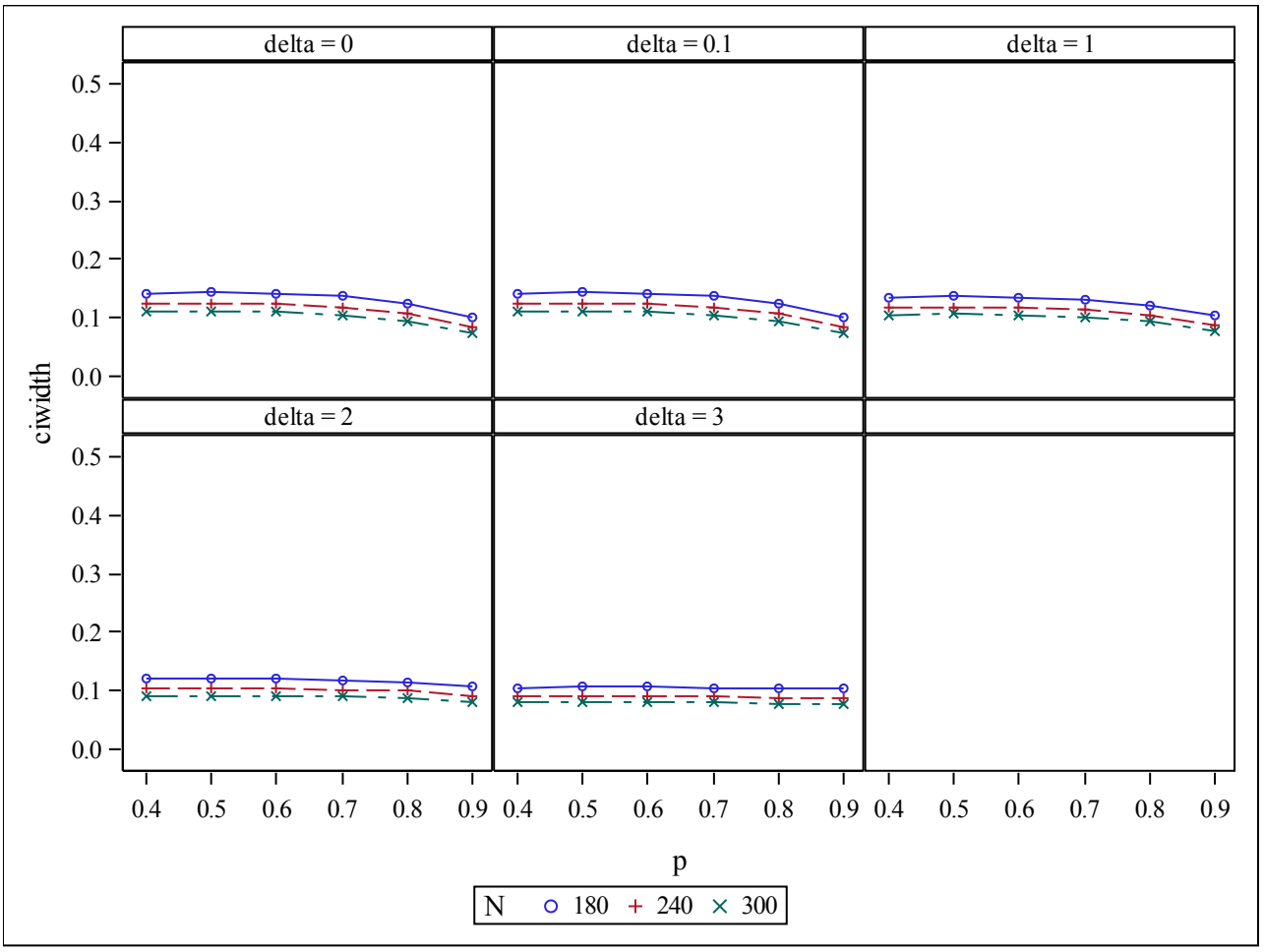

Figure 2: 90th percentile for the 95% confidence interval widths of the estimate of implementation success rate as a function of the true value (p) for given site variability, delta (Δ) and sample size, N.

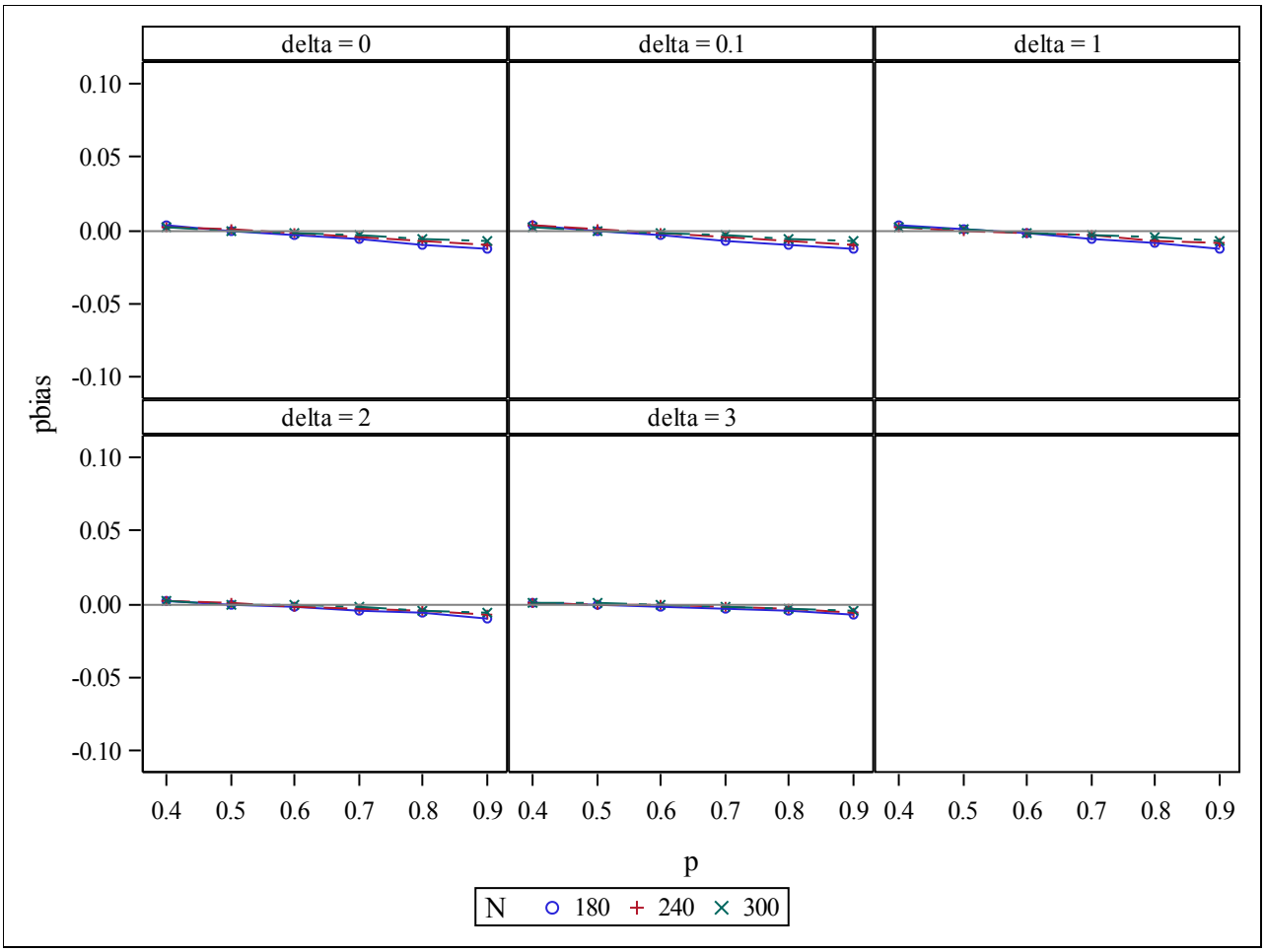

Figure 3: Mean bias for implementation success rate as a function of the true value (p) for given site variability, delta (Δ) and sample size, N.

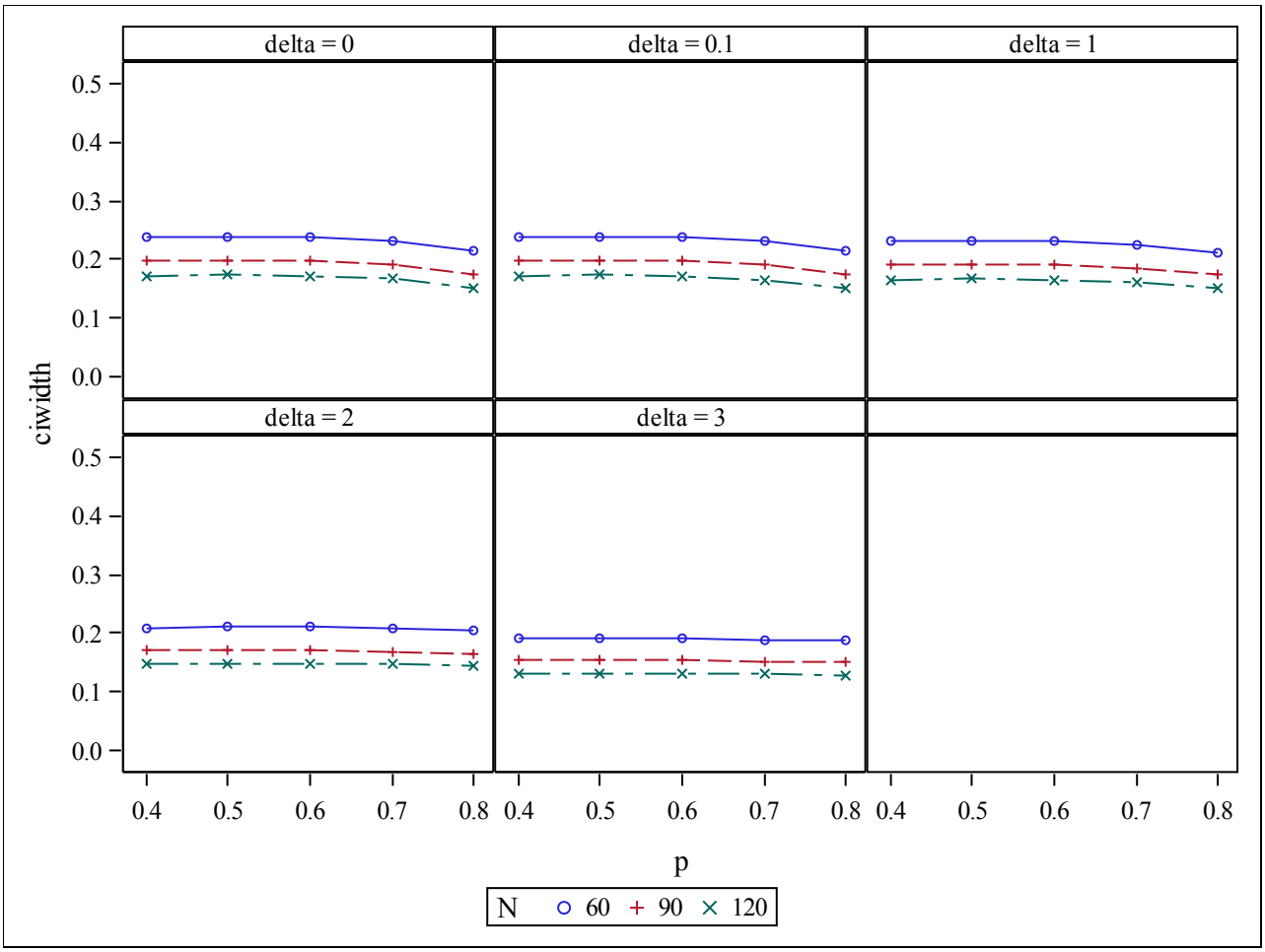

Figure 4: 90th percentile for the 95% confidence interval widths of the estimate of effectiveness success rate as a function of the true value (p) for given site variability, delta (Δ) and sample size, N.

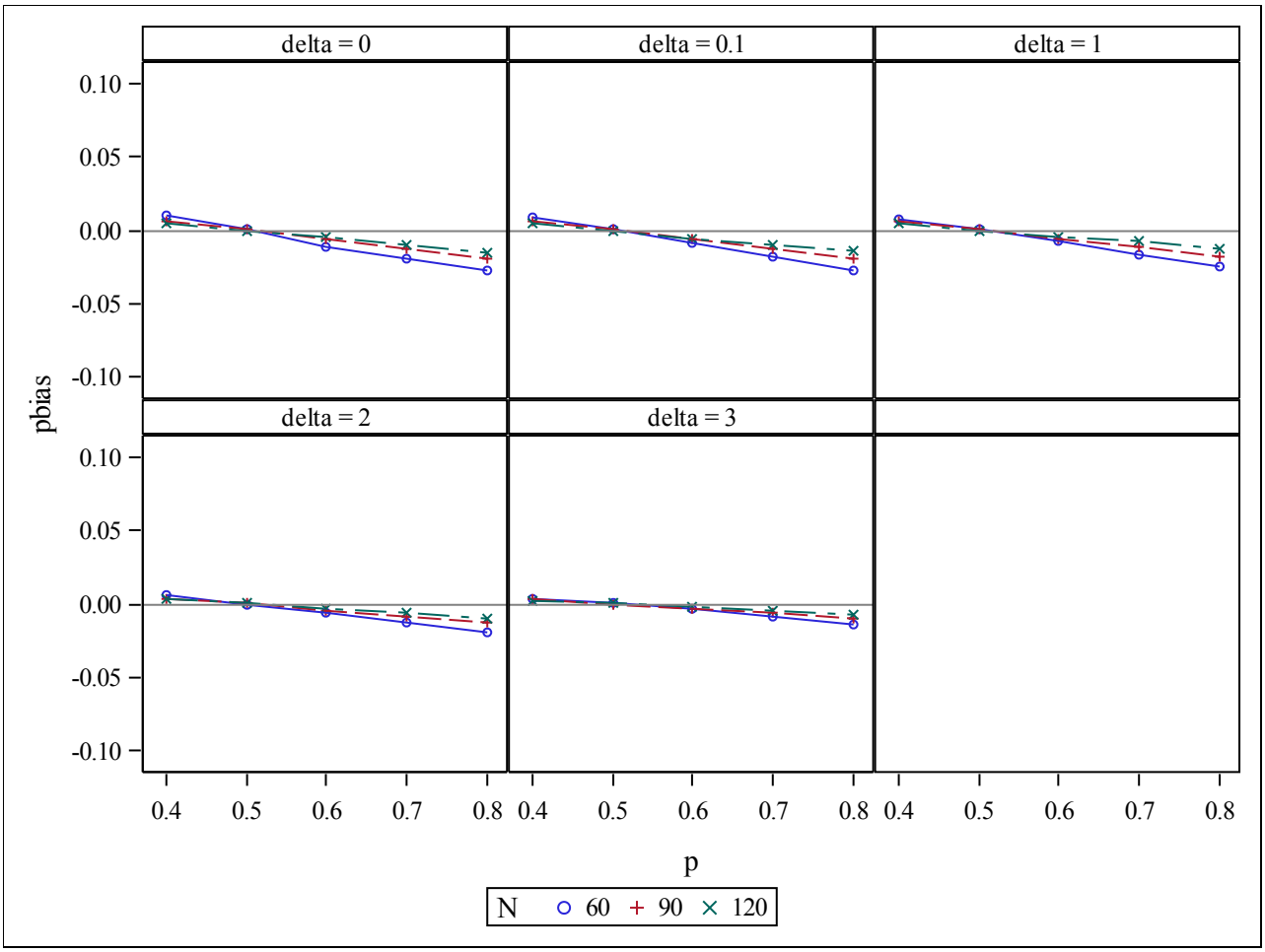

Figure 5: Mean bias for effectiveness success rate as a function of the true value (p) for given site variability, delta (Δ) and sample size, N.

12.5.3 Summary of Precision Analyses

For all the simulation scenarios investigated for primary implementation and effectiveness outcomes, the 90th percentiles of the 95% confidence interval widths seem to decrease with increase in site differences and are relatively lower for larger sample size; the planned sample sizes of N=300 (ED patients) and N=120 (participants), but are all below 0.2 and 0.3 for implementation and effectiveness probabilities, respectively. This means for each scenario investigated, 90% of the confidence interval widths are less than 0.2 and 0.3, respectively. The narrow confidence widths imply that, the estimated success rates are good representatives of the true implementation and effectiveness probabilities. There is minor downward bias that seems to diminish with increase in site differences for the implementation probability and effectiveness probability, but the bias is minimal for all the scenarios investigated. In summary, for the planned sample sizes, and for all scenarios investigated, the estimates for the primary implementation and effectiveness outcomes have small bias and capture the true outcomes with high precision.

12.6 Secondary Analysis

Secondary implementation outcomes will be analyzed using descriptive statistics such as proportions, counts/frequencies with 95% confidence intervals and univariate tests like Chi-Square/Fisher exact test t-test and nonparametric tests, where appropriate. Similarly, secondary

effectiveness outcomes will be analyzed using appropriate summary statistics and univariate tests. Statistical models such as Generalized Linear Models (GLM) and Generalized Estimating Equations (GEE) with appropriate distributions and link functions, and Linear Mixed Models (LMM) may be used to analyze some secondary outcome measures where appropriate.

12.7 Tertiary and Exploratory Analysis

These will include (1) evaluating implementation and effectiveness outcomes over the course of the CTN-0079 parent and CTN-0079-A1 ancillary studies and conducting comparisons between each of the defined 6-month Implementation (i.e., parent study), Post-IF, and Maintenance Periods for which comparable data exists; (2) Testing several permutations of the primary implementation and effectiveness outcomes. For example, (i) permutations of how the numerator or denominator are defined and how these data are collected for the primary implementation outcomes (e.g., excluding referrals; including only patients identified through EMR documentation) (ii) permutations to effectiveness outcomes and analyses will include evaluation of linkage and engagement over different timeframes (e.g., linkage within 72 hours, 14 days, and 30 days; time-to-event analyses), evaluating alternative denominators (e.g., including participants who did not receive ED-initiated BUP), and alternate means of how these data are captured and defined (e.g., claims and other administrative data). Other analyses will include comparing the agreement of quality measures assessed using administrative data to the gold standard data collected through the clinical research assessments and identifying patient-level characteristics as well as structural and process measures associated with measure completion and effectiveness. See section 8.3 for more details on tertiary and exploratory outcomes.

Analyses of tertiary and exploratory outcomes may use the same approaches used for primary and secondary outcomes. Additionally, time-to-event analyses may be conducted for linkage and engagement time-to-event outcomes.

12.8 Significance Testing

Analyses for primary implementation and effectiveness analyses are descriptive in nature hence no anticipated adjustment for multiple testing. Likewise, no adjustments for multiple comparisons for the secondary and exploratory analyses as this is a feasibility study. Instead, the type I error rate will be controlled at 5% for all statistical testing.

12.9 Interim Analysis

Interim analysis will be conducted at the end of the Post-IF Period to determine if the study should proceed as planned - without additional IF support – into the Maintenance Period. The analysis will be conducted by site and will compare the rates of ED-initiated BUP during the parent study enrollment period and the Post-IF period of the ancillary study. The ED-initiated BUP measure will include BUP administered or prescribed in the ED, as warm handoffs to BUP treatment within 24 hours were not included in the operational definition of the ED-initiated BUP measure for the parent study. Sustainability will be declared to have failed if the treatment initiation rate in the Post-IF period is <25% of that observed during the parent study with the qualification that warm handoffs to a BUP provider for treatment within 24 hours do not become a primary means of treatment for a site, such that inclusion of this outcome would significantly affect the analysis and change the conclusion. If failed sustainability is met, the study team will resume IF support at the site(s) and data collection and enrollment will continue; however, by definition, it will no longer be considered a Maintenance Period. As such, statistical analyses and reporting would be amended accordingly.

12.10 Missing Data

There will be no loss to follow-up for the primary implementation outcomes, because they are assessed almost immediately on ascertaining that the individual is a candidate for ED-initiated BUP.

With respect to the primary effectiveness outcomes, participants lost to follow-up after receiving ED-BUP will be counted as not linked or engaged (failure) in treatment instead of generating missing data. Sensitivity analyses may be conducted whereby participants lost to follow-up after receiving ED-BUP will be counted as missing data and the results compared with the above approach where such cases are considered as failure.

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

12.11 Demographic and Baseline Characteristics

Participants' and ED providers' baseline demographics and characteristics will be presented using summary statistics. Distributions of continuous variables will be presented with mean and standard deviation. Categorical variables will be summarized in terms of frequencies/counts and percentages.

12.12 Safety Analysis

The following events will be summarized by site: opioid-related overdose events, healthcare utilization including ED visits and hospitalizations, suicidal ideation, and death events. The assessment period for these events will begin at the time of participant consent and end with participant study completion at the Day 30 visit.

12.13 Qualitative Statistical Analyses

We will utilize the Rapid Assessment Process[15] a type of participatory action research using intensive, team interaction and multiple cycles of data collection followed by data review and analysis. It is estimated that 2-3 events, either by focus group or individual interview, will occur until themes begin to repeat.

Using directed content analysis[29], transcripts will be independently reviewed, coded and analyzed by a multi-disciplinary group. Initially transcripts will be individually reviewed line by line in entirety and coded by multiple independent team members. Following the coding of the initial set of transcripts, the qualitative research team will meet to review the initial coding scheme and a codebook will be generated by consensus, which will contain operational definitions for each code. Code generation will be iterative and the codebook subject to change until no new codes are identified. Common patterns across the dataset will be identified and will be grouped into themes. Analysis will use the PARiHS framework, which examines the interaction between three key elements of Evidence, Context and Facilitation, and including sub-elements of patient and clinical experience (communication, knowledgeable and empathetic providers), receptive context (resources to provide addiction treatments), and culture (value of team-based approach). An audit trail will be maintained. Data will be entered into and organized using Atlas.ti software. Participant feedback on analysis will be sought in follow-up interviews to enhance the validity of our findings.

We will also use the technique of triangulation, in which the data from different types of ED and community staff and providers, including nursing, social work, administrators, physicians, physician assistants and advanced nurse practitioners are interpreted in the context of each other and patient perspectives to better understand facilitators and barriers. In addition to triangulating by different sources of qualitative data, data will be interpreted in the context of other types of data available, including data abstracted from EMR and administrative databases, and quantitative data from participant assessments.

13.0 REGULATORY COMPLIANCE AND SAFETY

13.1 Statement of Compliance

This trial will be conducted in accordance with the current version of the protocol, in full conformity with the ethical principles outlined in the Declaration of Helsinki, the Protection of Human Subjects described in the International Council for Harmonisation 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 Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. An Operations Manual will be provided as a reference guide and study quality assurance tool.

13.2 Institutional Review Board Approval

The Biomedical Research Alliance of New York (BRANY) will be the IRB of record for the protocol and will provide study oversight in accordance with 45 CFR 46. Participating institutions have agreed to rely on BRANY IRB and have entered into reliance/authorization agreements for Protocol CTN-0079-A1. BRANY IRB will follow written procedures for reporting its findings and actions to appropriate officials at each participating institution. Some sites may meet Exception Criteria to the NIH single IRB Policy and may not utilize the IRB of Record.

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 involving risk to study participants will be promptly reported to and reviewed by the IRB of record, according to its usual procedures.

13.3 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 written informed consent form for Full Study participants will include all the required elements of informed consent and may contain additional relevant consent elements and NIDA CCTN specific additional elements. Each study site must have all study informed consent forms (written and verbal) approved by the IRB of record. Prior to initial submission to the IRB and with each subsequent consent revision, the consent form(s) must be sent to the Clinical Coordinating Center

(CCC) and the Lead Node (LN) 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, or for Limited Study Participants, a signed, Information Sheet, in addition to study-specific Release of Information form prior to the initiation of any study related procedures. Every Limited Study participant will be presented with an Information Sheet to be reviewed and signed prior to participation. The site must maintain the original signed the applicable consent documents (i.e., ICF, Information Sheet) for every participant in a locked, secure location that is in compliance with all applicable IRB and institutional policies and that is accessible to the study monitors. Note: Authorization is embedded within the Informed Consent form and the Information Sheet. Every focus group and qualitative interview participant will verbally consent to participation. Each participating site will request a Waiver of Documentation of Informed Consent.

During the informed consent process, research staff will explain the study to the potential participant and provide the potential participant with a copy of the informed consent form to read and keep for reference. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and their rights as research participants. Extensive discussion of risks and possible benefits will be provided to the participants. Participants will have the opportunity to carefully review the written informed 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 signing and dating the consent document. The person obtaining consent and a witness, if required by the IRB of record, will also sign and date the consent document. It is strongly recommended that another research staff member review the consent after it is signed to ensure that the consent is properly executed and complete. Staff members delegated by the site PI to obtain informed consent must be listed on the Delegation of Responsibility and Staff Signature (DoR) Log and must be approved by the IRB, if required. All persons obtaining consent must have completed appropriate GCP and HSP training, as mandated by NIDA standard operating procedures.

The informed consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect participants' participation in the trial. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The participant will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason without penalty. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice. Study sites will be responsible for maintaining signed consent forms as source documents for quality assurance review and regulatory compliance.

Each participating site will request a Waiver of Informed Consent/HIPAA authorization from the IRB of record for the abstraction of data from the medical record and for the linking of these patient data to registry, administrative and claims data. Each participating site will request a Waiver of Documentation of Informed Consent for the completion of the ED Health Survey.

In accordance with applicable federal regulations (45 CFR 46.116(f)), the study protocol meets the following required criteria as defined in 45 CFR 46.116(f)(3)):

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

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

13.4 Quality Assurance and Safety 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, monitoring of drug disposition, 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.

13.5 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 and the participant.

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

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), 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 at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as denoted in Section 13.8, Records Retention and Requirements.

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

13.5.1 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.

13.5.2 Health Insurance Portability and Accountability Act (HIPAA)

Study sites may be required by their institutions to obtain authorization from participants for use of protected health information. Sites will be responsible for communicating with the IRB(s) or Privacy Board(s) 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.

13.5.3 Investigator Assurances

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

13.5.4 Financial Disclosures

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.

13.5.5 Clinical Monitoring

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

NIDA-contracted monitors will assess whether submitted data are accurate and in agreement with source documentation and will also review regulatory/essential documents such as correspondence with the IRB of record. 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 study. Reports will be prepared following the visit and forwarded to the site principal investigator, the Lead Investigator (LI) and NIDA CCTN.

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

13.6 Special Populations to Consider

13.6.1 Inclusion of Women and Minorities

The study sites 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 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.

13.6.2 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. In order to meet these additional protections, the study team will obtain certification from the Office for Human Research Protections (OHRP) to follow-up with participants who become prisoners during the course of the study, as necessary.

Approval from the Office for Human Research Protections (OHRP) to include prisoners at the time of the Day 30 follow up visit will be obtained.

Data may be collected either in person, by phone, in writing, and/or by electronic means, provided that data collection follows the procedures approved by OHRP and the IRB of record. Details of the nature of the research will not be shared with staff at the jail/prison, and visits, whether in person or by phone, will only be conducted if the participant's confidentiality can be maintained and no audio-taping occurs. Study participation will have no effect on the participant's jail/prison sentence, nor potential probation or parole.

13.6.3 Employees

The study will include employees of the sites and local community treatment programs. A subset of those meeting eligibility criteria will be invited to participate. Extra caution will be taken to ensure participants are neither pressured nor coerced. Declination to participate will not affect their careers and credits.

13.7 Regulatory Files

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

13.8 Records Retention and Requirements

Research records for all study participants (e.g., case report forms, source documents, signed consent forms, audio and video recordings, and regulatory files) are to be maintained by the investigator in a secure location for a minimum of 3 years after the study is completed and closed. These records are also to be maintained in compliance with IRB, state and federal requirements, whichever is longest. The Sponsor and LI 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.

13.9 Reporting to Sponsor

The site PI 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 LI will provide a final report to the Sponsor.

13.10 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 LI and authorized staff from the National Lead Study Team; 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.

13.11 Study Documentation

Each participating site will maintain appropriate study documentation (including medical and research records) for this trial, in compliance with ICH E6 R2 and regulatory and institutional requirements for the protection of confidentiality of participants. Study documentation includes all

case report forms (CRFs), workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or IRB correspondence and approved consent forms (written and verbal) and signed participant consent forms. As part of participating in a NIDA-sponsored study, each site will permit authorized representatives from NIDA and regulatory agencies to examine (and when permitted by law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document. As per Section 10.11, to maximize confidentiality and minimize opportunity of inadvertent voice recognition, audio recordings on the recorder will be destroyed following their transcription, and recordings on the secured storage drive will be maintained until the transcripts are reviewed in their entirety and no questions related to inaudible or inaccurately transcribed portions remain. These recordings will subsequently be destroyed.

13.12 Approach to the Use of Administrative Data

Our approach to the use of administrative data for our research purposes described herein will be based on established best practices and ethical guidelines and organized under the following four principles or parameters: 1) security of the data; 2) confidentiality of information contained in the data; 3) permission to use data for research purposes; and 4) appropriate/ethical use of the data by the researchers.[11, 30] We will secure data in accordance with applicable laws (e.g., HIPAA, CFR 42 Part 2,) establish security protocols based upon industry standards, summarized by organizations such as the CERT Coordination Center at Carnegie Mellon[31] University or the System Administration, Networking and Security Institute (SANS Institute).[32] The security plan include (1) well-trained staff, ensuring that all people who have access to, or can grant access to, sensitive data must understand the risks involved with disclosure of information and have the expertise to secure the data. Second, we will establish well-crafted policies and procedures that provide clear processes for ensuring that data are secure based on available models for security guidelines and policies (e.g., SANS Institute). Third, in consultation with experts to confirm current options and industry standards, we will use technological safeguards, including data encryption, secure network controls (e.g., logged firewalls, two-factor access protocols).

It is of critical importance to ensure patients' rights to privacy and confidentiality are appropriately preserved and that permissions are secured when linking patient-level data to administrative data, particularly data related to substance use services (with the added protections under CFR 42 Part 2). As such, prior to linking data with covered entities, we will establish data usage agreements and will maintain strict adherence to legal and ethical standards and best practices.

We will obtain appropriate permissions to retain, access, and use administrative data. We will make a formal and detailed request for data from the data owner/custodian. This request will include things such as an introduction to the study, a list of needed variables, timespan and population parameters for the data, transfer media/methods, and a checklist for owner/custodian staff to follow to ensure better accuracy of data extraction. The written agreement with the data owner/custodian will clarify the terms of data possession and what analyses and studies are allowed using the data, how the data will be secured and confidentiality maintained, whether additional permissions or consent will be required at an individual level, and how long we may retain the data. The agreement will also address with whom we may share the data (if anyone).

More specifically, we have pending data use agreements with the NH DHHS and NYU HEAL, who are custodians of Medicaid claims data and other administrative data for NH and NY, respectively. Although the terms of the data use agreements are not finalized and subject to some modifications, a general overview of the data sharing/linkage process is as follows. We (study coordinators/staff) will create a data set containing the identifiers necessary for the match (name, DOB, sex/gender, medical record number, etc.) as well as a unique identifier for patients who present to the EDs who are identified to have opioid use. As it is not feasible to contact the large volume of patients treated in the ED to obtain individual authorizations, particularly among individuals without stable phone access or addresses, we request a waiver of consent. Through this waiver, we will share this data set with the covered entity that is the owner/custodian, which will include but not be limited to the NH DHHS and NYU HEAL. In accordance with the data use agreement, they will use the data set to perform the match with Medicaid claims (and potentially other administrative data, pending availability) and/or grant permission to a study staff/data analyst to perform the match. The identifiers contained in the original data set (name, DOB, etc.) with the exception of the unique identifier, will be expunged from the new data set and not re-linked by the study team. Administrative data will, however, be linked through the unique identifier to the assessments, outcomes, and other data of the Limited Study and Full Study participants who provided individual written authorization.

The administrative data matching will allow us to evaluate outcomes for the larger population of patients who present to the ED with OUD. It is essential to evaluate the entire population of patients with untreated OUD to ensure equity in the larger effort to improve quality of care and treatment outcomes at the population level. It is well-aligned with our overall goal to inform the development and improve the effectiveness and reach of programs that identify and initiate treatment of OUD in EDs in a way that is generalizable to support population-level health quality improvement and treatment outcomes.

13.13 Protocol Deviations

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

These practices are consistent with ICH GCP:

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

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

(1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial.

All protocol deviations will be recorded in the Electronic Data Capture (EDC) system via the Protocol Deviation CRF. The CCC, DSC and the LI must be contacted immediately if an unqualified or ineligible participant is enrolled into the study.

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

13.14 Safety Monitoring

The LI may appoint a Site Medical Clinician (MD, DO, NP, or PA) for this study, who will review or provide consultation for each Safety Event and Serious Adverse Event (SAE) as needed. Adverse Events (AEs) other than defined Safety Events will not be tracked or reported. For the purposes of this protocol, the only SAEs that will be tracked, reviewed, and reported are those associated with death, which will include any participant death occurring during the study or which comes to the attention of the study staff during the protocol-defined follow-up period, whether or not considered caused by the study intervention. These reviews will include an assessment of the possible relatedness of the event to the study intervention or other study procedures. The Site Medical Clinician will also provide advice for decisions to exclude, refer, or withdraw participants as required. In addition, A Safety Monitor/Medical Monitor will be assigned to independently review the safety data, present it to the DSMB for periodic review, and provide PIs a Safety Letter when necessary. The Safety Monitor/Medical Monitor will determine which safety events require expedited reporting to NIDA, the DSMB and regulatory authorities. This will include events that are serious, related and unexpected. The study staff will be trained to monitor for and report Safety Events and death-related SAEs.

Each of the sites has established practices for managing medical and psychiatric emergencies, and the study staff will continue to utilize these procedures. Treatment providers at each site will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

13.14.1 Data and Safety Monitoring Board (DSMB)

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

13.14.2 Safety Monitor/Medical Monitor

The CCC Safety Monitor/Medical Monitor is responsible for reviewing all Safety Events and death-related serious adverse events reported. All death-related SAEs will be reviewed within one business day of being reported in the eClinical. The Safety Monitor/Medical Monitor will also indicate concurrence or not with the details of the report provided by the site. Where further information is needed, the Safety Monitor/Medical Monitor will discuss the event with the site. Reviews of death-related SAEs will be conducted in the Advantage eClinical data system and will

be a part of the safety database. All Safety Events are reviewed on a regular basis to observe trends or unusual events.

The CCC Safety Monitor/Medical Monitor will in turn report events to the sponsor and regulatory authorities if the event meets the definition of an expedited event. Reports will be generated and presented for Data Safety Monitoring Board (DSMB) meetings.

13.14.3 Safety Events

Because this prospective study will examine BUP treatment initiation and the impact of ED-initiated BUP on engagement in addiction treatment and drug-use-related outcomes, and the use of these medications is in line with community practice, safety reporting will be limited to recording any opioid overdose that occurs on study, any death, suicidal ideation, and healthcare utilization including ED visits and hospitalizations. Deaths will be reported on the adverse/serious adverse event form set. The other Safety Events will be reported on study specific forms.

For the purpose of this study, the following events will not be reported as SAEs but will instead be reported on study-specific forms. These events will be reported to the single IRB (and any local IRB(s), if applicable) per IRB guidelines:

- Opioid overdose (not resulting in death)
- Suicidal ideation (not resulting in death)
- Healthcare utilization including ED visits and hospitalizations

Each of the sites and communities have established practices for managing medical and psychiatric emergencies, and those established practices will be followed per standard of care in each community. When a medical or psychiatric emergency is identified, including presence of potential suicidal ideation, research staff will activate local procedures to ensure participant safety. As there is no planned interaction between limited study participants and research staff post enrollment, research staff will not actively intervene when safety events are identified in limited study participants.

14.0 DATA MANAGEMENT AND PROCEDURES

14.1 Design and Development

This protocol will utilize a centralized Data and Statistics Center (DSC) for all quantitative data collected in the project. Qualitative data will be managed and stored by Yale University, as described in Section 10.10. The DSC will be responsible for the development of the CRFs, development and validation of the clinical study database, ensuring data integrity, and training site and participating node staff on applicable data management procedures. Advantage eClinical, a web-based distributed data entry system, will be implemented. This system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld. The remainder of this section provides an overview of the data management plan associated with this protocol.

14.2 Site Responsibilities

The data management responsibilities of each individual site will be specified by the Lead Node and by the DSC and outlined in the Advantage eClinical User's Guide.

14.3 Data Center Responsibilities

The DSC 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 for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) conduct ongoing data monitoring activities on study data from all participating sites, 5) monitor any preliminary analysis data cleaning activities as needed, and 6) rigorously monitor final study data cleaning.

14.4 Data Collection

Data will be collected at the study sites either on source documents, which will be entered at the site into eCRFs, or via direct entry into the eCRF. eCRFs are to be completed on an ongoing basis during the study. In the event that Advantage eClinical is not available, the DSC will provide the sites with paper guided source documents and completion instructions. Data entry into Advantage eClinical 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.

14.5 Data Acquisition and Entry

Completed forms and electronic data will be entered into the Advantage eClinical system in accordance with the Advantage eClinical User's Guide, the CRF Instructions Manual and relevant instructions in the study operations manual. Only authorized individuals shall have access to eCRFs.

14.6 Data Editing

Completed data will be entered into Advantage eClinical. If incomplete or inaccurate data are found, a query will be generated to the sites for a response. Sites will resolve data inconsistencies and errors and enter all corrections and changes into Advantage eClinical.

14.7 Data Transfer/Lock

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DSC. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by DSC staff will be secured and password protected. Data will be transmitted by the DSC to the NIDA central data repository as requested by NIDA. The DSC will conduct final data quality assurance checks and "lock" the study database from further modification. The final analysis dataset will be returned to NIDA, as requested, for storage and archive.

14.8 Data Training

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

14.9 Data Quality Assurance

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

15.0 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 13.5.

16.0 PROTOCOL SIGNATURE PAGE

SPONSOR'S REPRESENTATIVE (CCTN SCIENTIFIC OFFICER OR DESIGNEE)

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 2.0 of the protocol and agree to conduct this clinical study in accordance with the design and provisions specified therein.

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

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

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

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

SITE'S PRINCIPAL INVESTIGATOR

Printed Name	Signature	Date

Clinical Site Name _____

Node Affiliation _____

17.0 REFERENCES

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18.0 APPENDIX A: DATA AND SAFETY MONITORING PLAN

1.0 BRIEF STUDY OVERVIEW

CTN-0079-A1 will evaluate the extent of diffusion and the sustainability of the Emergency Department (ED)-initiated buprenorphine (BUP) clinical programs (inclusive of opioid use disorder [OUD] screening, BUP treatment initiation, and referral for treatment) introduced at each of the three clinical sites in the parent CTN-0079 study in furtherance of our original overarching research question: *In settings with high need, limited resources, and differing staffing structures for managing OUD, what is the feasibility and impact of introducing a clinical protocol for OUD screening and BUP treatment initiation in the ED with referral for treatment?* CTN-0079-A1 (the "ancillary study") is an implementation study that will use mixed methods and triangulate multiple sources of data to evaluate the feasibility, acceptability, sustainability, and impact of the ED-initiated BUP clinical program and implementation facilitation strategy and identify factors influencing diffusion and effectiveness.

PRIMARY AIMS

1. Program Implementation (Evaluation of Clinical Program Reach): Over the course of the CTN-0079-A1 study, to estimate the proportion of patients receiving (i) ED-initiated/expedited BUP (primary analysis) and (ii) ED-initiated BUP (secondary analysis) amongst ED patients who are candidates for ED-initiated BUP. The composite ED-initiated/expedited measure will be analyzed primarily; ED-initiated BUP will be evaluated secondarily.
2. Program Effectiveness: Amongst participants who received ED-initiated/expedited BUP over the course of the CTN-0079-A1 study, to estimate the proportion of participants: (*i*) with confirmed linkage to formal addiction treatment for OUD within one week following ED discharge, and (*ii*) who are confirmed to be engaged in formal addiction treatment for OUD on the 30th day following ED discharge. Engagement in treatment on day 30 will be analyzed primarily; linkage will be evaluated secondarily.

Other Aims: We will also conduct several secondary implementation and effectiveness analyses as well as tertiary and exploratory analyses that include periods within the parent and ancillary studies and comparing available sources of data to further develop quality measures.

SOURCES OF DATA

1. Health record, administrative, claims, and registry data
2. Research assessments involving ED patients who are candidates for ED-initiated BUP for OUD; these assessments will document the index ED visit through the 30th day after the index ED visit
3. Qualitative data (qualitative interviews, focus groups, field notes) involving ED staff, ED patients, and other stakeholders and key informants
4. Data collected through the CTN-0079 "parent" study
5. Qualitative data collected through CTN-0069

As in CTN-0079 (the "parent study"), all clinical care (BUP and referral) will be delivered as part of each facility's clinical protocol, rather than as a research procedure. Implementation Facilitation (IF) activities will continue during ancillary trial preparation with a more intensive "booster" of IF

activities occurring in the last month prior to trial commencement. Thereafter, all study IF support will cease and ancillary study data collection will begin. Data collection will occur over a course of approximately 12 months, divided into two 6-month study periods – the Post-IF and Maintenance Periods. In accordance with the **RE-AIM framework** (Reach, Effectiveness, Adoption, Implementation, Maintenance), at minimum, a period of at least 6 months should separate the beginning of the Maintenance Period from the time of last study intervention. Study activities will be unchanged between these two periods. In this new trial, the implementation outcomes and related measurement methods have been adapted from those used in the parent study to incorporate lessons learned. Thus, primary outcome analyses will use data from the ancillary study alone. Tertiary and exploratory analyses will incorporate data from the 6-month period of patient enrollment of the parent study – that is, the IF Period – as well as data derived from linkage to administrative databases extending over a longer timeframe (from one year prior to patient/participants' ED visit to two years following the ED visit/enrollment).

ED patients who are candidates for ED-initiated BUP (and who meet the additional study eligibility criteria to become research participants) may be enrolled as Full Study or Limited Study participants. Full Study participation involves two in-person research visits occurring ideally at the index ED visit and 30 days after ED discharge, as in the parent study. In addition, consenting participants will be asked to authorize study staff to perform a data match with health and administrative data pending data use agreements for a period beginning 1 year prior to enrollment and ending 2 years following study enrollment. Limited Study participation will be offered to candidates who meet criteria for ED-BUP candidacy but do not meet all of the eligibility criteria (e.g., inadequate locator information) for Full Study participation. Limited Study participation includes completion of screening assessments and data matching only, without active participation in the baseline and day 30 research visits. In addition, a Waiver of Consent/HIPAA Authorization is requested to perform data matching for all adult ED patients who screen positive for non-medical opioid use during the study data collection period. Analyses will also be conducted for subgroups, including those determined to be candidates for BUP and/or receive medication for OUD, among others.

In addition, we will recruit ED staff, patients, and other stakeholders and key informants to be participants in qualitative interviews and/or focus groups at the close of study for the purpose of learning about patient-, provider-, and organizational-level barriers and facilitators to adoption and sustainability. These data (along with qualitative data collected through CTN-0069 and CTN-0079) will provide context to study outcomes and allow us to more comprehensively address our primary research question.

2.0 OVERSIGHT OF CLINICAL RESPONSIBILITIES

A. Site Principal Investigator

Each participating site's Principal Investigator (PI) is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified, trained research staff to assess, report, and monitor safety events.

Because this prospective study will examine BUP initiation, and the use of this medication is in line with community practice, safety reporting will be limited to recording opioid non-fatal overdose events, healthcare utilization including ED visits and hospitalizations, suicidal ideation, and all deaths including fatal overdoses will be tracked within the 30 days between the index ED visit and Day 30.

These safety events occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the Protocol. Since BUP is

provided consistent with community practice, a medication adverse event profile will not be maintained.

Non-fatal opioid overdoses will be assessed at each visit during the study and collected on the Overdose Events and Risk Factors form. Safety events resulting in death including fatal overdoses are required to be entered into the adverse/serious adverse event form set in the data system within 24 hours of site's knowledge of the event. The other safety events will be reported on study specific forms.

B. CCC Safety Monitor/Medical Monitor

The NIDA CTN Clinical Coordinating Center's (CCC) Safety Monitor/Medical Monitor or designee is responsible for reviewing all adverse events and serious adverse events reported. The CCC Safety Monitor/Medical Monitor is alerted via email each time an SAE is reported in the EDC. All SAEs will be reviewed at the time they are reported in the EDC. The Safety Monitor/Medical Monitor or designee will also indicate concurrence or not with the details of the report provided by the site PI. Where further information is needed, the Safety Monitor/Medical Monitor or designee will discuss the event with the site staff. Reviews of SAEs by the CCC Safety Monitor/Medical Monitor or designee will be documented in the Advantage eClinical data system and will be a part of the safety database. All AEs are reviewed on a weekly basis to observe trends or unusual events.

Voluntary Regulatory Reporting in non-IND Trials:

For non-IND trials, if an event meets expedited reporting criteria (serious, related and unexpected) the CCC Safety Monitor/Medical Monitor or designee will voluntarily report to FDA/Regulatory Authorities using the MedWatch Form 3500 or similar.

C. Data and Safety Monitoring Board (DSMB)

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

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

D. Quality Assurance (QA) Monitoring

The monitoring of the study site(s) will be conducted on a regular basis using a combination of NIDA CCTN CCC monitors and the local Node QA Monitors. Investigators will host periodic visits for the NIDA CCTN CCC monitors and local Node QA Monitors. The purpose of these visits is to assess compliance with the protocol, GCP requirements, and other applicable regulatory requirements, as well as to document the integrity of the trial progress. The investigative site will provide direct access to all trial related sites (e.g., research office), source data/documentation, and reports for the purpose of monitoring and auditing by the monitors, as well as for inspection by local and regulatory authorities. Areas of particular concern will be the review of inclusion/exclusion criteria, participant Informed Consent Forms, protocol adherence, safety

monitoring, IRB reviews and approvals, regulatory documents, participant records, and Principal Investigator supervision and involvement in the trial. The monitors will interact with the site staff to identify issues and re-train the site as needed to enhance research quality.

Site Visit Reports will be prepared following each site visit, as applicable. These reports are send to those entities required of them by the Lead Investigative team, generally including Lead Investigator, site Principal Investigator, Node PI and a CCC representative, usually the protocol specialist for the study.

Local Node site visit reports are sent to those entities required of them by the Lead Investigative team, generally including the Lead Investigator, Lead PM, site Principal Investigator, Node PI and a CCC representative, usually the protocol specialist for the study.

E. Management of Risks to Participants

Confidentiality

Confidentiality of participant records will be secured using 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

This is a minimal risk observational study that will use mixed methods and triangulate multiple sources of data to evaluate the feasibility, acceptability, sustainability, and impact of the ED-initiated BUP clinical program and implementation facilitation strategy and identify factors influencing diffusion and effectiveness. Patients will be evaluated for BUP administration as per local clinical guidelines.

Pregnancy

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

Recruitment Monitoring

Participant recruitment and achievement of targets will be closely monitored on an ongoing basis throughout the duration of both data collection periods. Trial progress and data status reports (Section 19.9) will be reviewed frequently (e.g., daily) by the Lead Node and discussed often (e.g., weekly) with the Lead Team. These reports will provide information on numbers screened and enrolled (by site and by RA), time and day of week of ED presentation, and numbers of enrolled participants receiving buprenorphine. This information will be used continuously throughout enrollment to inform recruitment shifts, staffing, and the need for additional training and support. All sites will be required to prepare a site-specific local SOP outlining recruitment procedures and a contingency plan should enrollment rates fall below target in any given month. After the first

three months of active recruitment (halfway through the Post-IF period) the Lead Team will have a formal review to identify recruitment trends and address any issues that arise.

3.0 DATA MANAGEMENT PROCEDURES

This protocol will utilize a centralized Data and Statistics Center (DSC) for all quantitative data. A web-based distributed data entry model will be implemented. This electronic data capture system (Advantage eClinical) will be developed to ensure that guidelines and regulations surrounding the use of computerized systems in clinical trials are upheld. All qualitative data will be stored on a password protected, encrypted university owned and secured computer.

4.0 DATA AND STATISTICS CENTER RESPONSIBILITIES

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

5.0 DATA COLLECTION AND ENTRY

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

The Principal Investigator at the site is responsible for maintaining accurate, complete and up-to-date research records. In addition, the Principal Investigator is responsible for ensuring the timely completion of eCRFs for each research participant. Audio recordings will be obtained using an encrypted recorder and transcribed by a professional HIPAA compliant transcription service.

Research staff, with oversight by the site PI, is responsible for maintaining accurate, complete and up-to-date research records. The site PI is responsible for ensuring the timely completion of eCRFs by research staff for each research participant.

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

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

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

7.0 DATABASE LOCK AND TRANSFER

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

At the conclusion of data collection for the study, the DSC will perform final data cleaning activities and will "lock" the study database from further modification. The final raw dataset will be transferred to the Lead Investigator or designee. De-identified versions of these datasets will also be provided to the NIDA CCTN-designated party for storage and archiving. These datasets maybe be posted on the NIDA Data Share website.

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