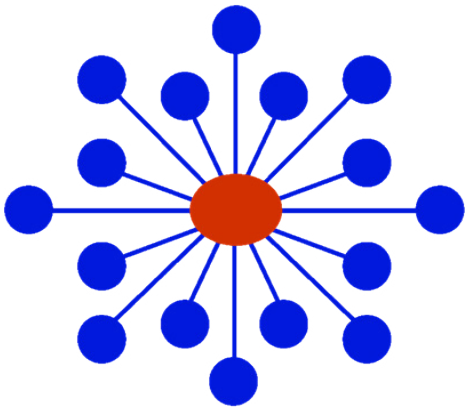

NIDA CTN-0079

Emergency Department Connection to Care with Buprenorphine for Opioid Use Disorder (ED-CONNECT)

Version 3.0

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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
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
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
EQ-5D	European Quality of Life – 5 Dimensions
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

Abbreviation	Definition
ICD	International Classification of Diseases
IF	Implementation Facilitation
IRB	Institutional Review Board
LI	Lead Investigator
LN	Lead Node
MD	Medical Doctor
MDMA	Methylenedioxymethamphetamine (Ecstasy)
ME	Medical Examiner
mg	Milligrams
MOP	Manual of Operating Procedures
NA	Narcotic Anonymous
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NP	Nurse Practitioner
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
PI	Principal Investigator
QA	Quality Assurance
SAE	Serious Adverse Event
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

2.0 STUDY SYNOPSIS

Our central research question is: In settings with high need, limited resources, and differing staffing structures for managing opioid use disorder (OUD), what is the feasibility and impact of introducing a clinical protocol for OUD screening and buprenorphine (BUP, either as sublingual [SL-BUP] or extended-release [XR-BUP]) treatment initiation in the Emergency Department (ED) with referral for treatment?

Aims:

1. To evaluate using mixed methods the feasibility and acceptability of OUD screening, ED- initiated BUP, and referral.
2. Over the course of the study and as XR-BUP is added to hospital formularies, to estimate the percentage and confidence intervals of patients assessed, treated, and engaged in treatment at Day 30.

This will be a three-site study employing a multi-faceted approach to facilitate clinical protocol implementation and to assess feasibility, acceptability, and impact. We will develop, introduce and update site-specific ED clinical protocols and implementation plans for OUD screening, ED-initiated BUP, and referral for treatment. We will employ a participatory action research approach and use mixed methods incorporating data derived from:

1. Medical record and administrative data abstraction,
2. Research assessments involving patients who are eligible for and willing to receive ED-initiated BUP (including both those who do, and do not, receive BUP); these assessments will document the index ED visit and the 30th day after the index ED visit,
3. Qualitative interviews, focus groups, and quantitative assessments involving providers and staff, patients, and other stakeholders.

The intervention itself (BUP and referral) will be delivered as part of the facility's clinical protocol, rather than as a research procedure. The clinical protocol will be updated on an ongoing basis via a continuous quality improvement (CQI) process. Data abstracted from the electronic medical record (EMR) will be used to assess process measures including the primary clinical outcome of proportion receiving ED-initiated BUP amongst those who are eligible for and willing to receive ED-initiated BUP. Secondarily, we will explore additional patient-level outcomes (engagement in ongoing treatment, drug use, overdose events, healthcare use, quality of life, etc.) by recruiting eligible and willing patients who received or did not receive ED-initiated BUP, to participate in two research visits. The baseline research visit, assessing clinical care received during the index ED 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, assessing engagement in treatment on the 30th day after the index ED 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. In addition, from each site, we will recruit ED and community providers and staff, ED patients, and other stakeholders to participate in qualitative interviews, focus groups, and quantitative assessments for the purpose of learning about patient-, provider-, and organizational-level barriers and facilitators to implementation and the resources needed to ensure that this intervention can be delivered in a way that is feasible, acceptable, and sustainable in these practice settings.

The study will proceed along a rapid 21-month timeline in keeping with the urgency of the opioid epidemic. (See Table 2: Estimated Project Timeline in Section 5: Study Design.)

This study will complement CTN-0069, an ongoing hybrid implementation-effectiveness study taking place in large, urban academic medical centers with rich existing resources and robust infrastructure to support ED-initiated BUP (SL-BUP only) and referral for ongoing OUD treatment.

3.0 INTRODUCTION

The opioid epidemic has reached a critical state, drawing widespread attention and support to address this public health crisis[1-3]. For many reasons, the Emergency Department (ED) is a critical venue to initiate opioid

use disorder (OUD) interventions. ED patients have a disproportionately high prevalence of substance use disorders, are at an elevated risk of overdose, and many do not access healthcare elsewhere[4, 5]. Despite this, OUD interventions are rarely initiated in EDs. The prevailing culture of the ED is that substance use disorders (SUDs) are non-emergent, chronic conditions better addressed outside the ED where resources are less limited. Lack of training, time, and definitive referral opportunities are frequently cited barriers[6]. Expertise, resources and training are often absent in rural communities. Public "safety net" hospitals also represent a unique context, having a high prevalence of patients with substance use problems complicated by psychosocial vulnerabilities, while operating with a fraction of the staff and ancillary support of private institutions. Research is urgently needed to clearly identify, develop, and implement the elements essential to initiating OUD treatment and referral in EDs in ways that are effective, practical and sustainable across settings and that are acceptable to patients, providers, healthcare agencies and payers.

Among efficacious pharmacotherapies for OUD[7-14], buprenorphine (BUP), a partial agonist at the mu opioid receptor, is the most practical option for treatment initiation in the ED. Through a 3-arm randomized trial of 329 opioid dependent patients, D'Onofrio et al., demonstrated the feasibility, safety, and efficacy of initiating SL-BUP in an urban academic ED along with providing enough take-home medication to last until a scheduled outpatient follow up appointment 24-72 hours later for ongoing medication treatment for OUD[15]. More broadly implementing ED-initiated SL-BUP is challenging as few ED providers have Drug Enforcement Agency (DEA) DATA 2000 registrations (aka X waivers) required to prescribe BUP (beyond what's permitted to be administered under the "3-day rule"). Given the culture of the ED, as described above, it is not reasonable to expect this will change appreciably. Further, outpatient providers able to accommodate urgent appointments – i.e., within a few days – are rarely available in most communities.

Novel injectable extended-release BUP formulations (XR-BUP) have the potential to provide longer- term coverage until outpatient care can be arranged, facilitate more widespread implementation and mitigate concerns related to diversion, misuse, and adherence[16]. Specifically, as the XR-BUP formulations produced by Braeburn Pharmaceuticals (CAM2038) are expected to be FDA-approved in 2018 without needing a lead-in period of SL-BUP prior to administration, this medication would be feasible for the ED. A single injection of XR-BUP provides coverage for a week or for a month (different formulations)[17, 18] allowing time for linkage to outpatient providers and at the same time initiating treatment and reducing overdose risk. Preliminary studies have shown XR-BUP to be safe and well- tolerated, simple to store and administer, with similar efficacy and dose-proportional BUP exposure compared to daily SL-BUP over its dosing interval[17].

The study by D'Onofrio et al., demonstrated that ED-initiated BUP with referral for ongoing BUP treatment is superior to referral alone for engaging and retaining patients in formal addiction treatment at 30 days(15). This study was conducted in an ED with robust ED resources, with research assistants to identify patients with moderate-to-severe OUD, a strong local champion (PI is chair of the ED), and dedicated study physicians to prescribe SL-BUP and provide ongoing medication treatment for OUD. The most effective methods for implementing these interventions across a variety of settings and under real-world conditions are unknown. Implementation Science, defined by the National Institute of Health as "the study of methods to promote the integration of research findings and evidence into healthcare policy and practice"(25), provides an organized approach and tools to fill the gap between the need and provision of ED-initiated BUP and ongoing medication treatment for OUD. For such a lofty challenge, it is appropriate to first study this in large, academic centers, with robust research and clinical infrastructure and capacity to provide ongoing medication, as is being done in CTN-0069 (Opioid Use Disorder in the Emergency Department [Project ED Health]), an ongoing implementation-effectiveness trial of ED-initiated SL-BUP. However, the opioid epidemic is indiscriminately decimating communities with differing community resources, payers, and other characteristics and these are served by EDs with differing patient volumes and capacities, staffing structures, institutional priorities, payer reimbursement rates, as well as material and intellectual resources (e.g., addiction specialists). Unfortunately, given the severity and lethal consequences of the opioid epidemic, we don't have time to sequentially learn best implementation practices under more ideal conditions (CTN-0069) and then learn how to translate them across various settings for more widespread adoption. This is where CTN-0079 comes in.

CTN-0079 builds on the aforementioned work by D'Onofrio et al., and CTN-0069, as an implementation feasibility study being conducted in settings with high need, limited resources, and differing staffing structures (ED and OUD treatment). The design, a modified implementation facilitation (IF) approach, and the very short timeframe reflect the compromises between the desire to achieve scientific rigor and the need to quickly implement treatment to address an urgent public health crisis. Specifically, we will adapt study methods being used in CTN-0069, including instruments for formative evaluation and assessments, to expedite clinical and research implementation and to facilitate comparisons across these studies being conducted in markedly different ED settings. Important distinctions from CTN-0069 include that we will introduce a clinical protocol that includes use of either SL-BUP or XR-BUP and that integrates clinical screening for OUD into the ED workflow. Integrating OUD screening will improve detection of study candidates, allow us to assess patient coverage and process measures more naturalistically and comprehensively by leveraging data collected in the EMR and/or paper charts, and minimize the potential influence of research staff screening on clinical care.

The opioid epidemic has a large and growing impact on public health, and continues to decimate communities ill equipped to provide substantive, timely intervention. As the receiving center for persons experiencing overdose, the call to action is reaching the ED. While the ED may be an ideal and underutilized venue for addressing this crisis, it is well-recognized to be an extremely challenging venue for introducing, sustaining, and studying interventions. By assembling subject matter experts and involving local stakeholders, we will translate successful elements of efficacious interventions to EDs operating in different contexts. These partnerships provide an opportunity for prompt, meaningful and sustainable dissemination with enhanced support for the intervention while it is being developed and tested in situ. This study is designed to provide the necessary, time-sensitive understanding of how to identify OUD and initiate treatment with BUP in the EDs where this intervention is most needed – which, if successfully done, should save lives, improve outcomes, and reduce costs to society.

4.0 AIMS AND OBJECTIVES

The overarching goal is to assess, in settings with high need, limited resources, and differing staffing structures for managing OUD, the feasibility and impact of introducing a clinical protocol for OUD screening and BUP (either as sublingual [SL-BUP] or extended-release [XR-BUP]) treatment initiation in the ED with referral for treatment.

Aims:

1. To evaluate using mixed methods the feasibility and acceptability of OUD screening, ED- initiated BUP and referral.
2. Over the course of the study and as XR-BUP is added to hospital formularies, to estimate the percentage and confidence intervals of patients assessed, treated, and engaged in treatment at Day 30.

5.0 STUDY DESIGN

5.1 Overview of Study Design

This is a multicenter, implementation feasibility study using mixed-methods combining qualitative and quantitative inquiry with administrative and health record data. We propose: (1) to develop, introduce and update site-specific clinical protocols and implementation plans to screen for and assess OUD, and where appropriate, (2) to initiate BUP (SL-BUP or XR-BUP) in the ED, and refer for ongoing treatment, (3) to employ a multifaceted approach to facilitate clinical protocol implementation, and (4) to assess feasibility, acceptability, and impact using mixed-methods. The modified formative evaluation approach and the very short timeframe reflect compromises between the desire to achieve scientific rigor and the need to quickly implement treatment to address an urgent public health crisis. The planned CQI measures using adapted Implementation Facilitation (IF) procedures as well as our planned analyses will inform the further development of the clinical protocols and implementation strategies to support sustainability and broader implementation across health systems.

Data will be 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 will conduct 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 will abstract data from the EMR and/or paper charts. Also, we will enroll patients who are eligible for and willing to receive ED-initiated BUP (both those who receive BUP and those who do not) to participate in assessments following their index visit to explore patient-level outcomes and learn about barriers and facilitators encountered during or associated with their actual experience in the ED.

Table 1: Research Components

	Key Informant Interviews	Focus Groups	ORCA / Change rulers	Learning Collaborative	EMR	Research Assessments	UDS
Implementation Outcomes							
Feasibility, acceptability, facilitators, barriers (ED and OUD treatment providers/staff)	X	X	X	X			
Feasibility, acceptability, facilitators, barriers (Community stakeholders)	X	X					
Feasibility, acceptability, facilitators, barriers (Patients)	X	X				X	
Clinical Protocol Outcomes							
Development	X						
Introduction	X	X			X		
Adherence/fidelity	X	X		X	X		
Quality improvement	X	X		X	X		
Patient Outcomes							
Opioid use					X	X	X
Safety					X	X	
Healthcare utilization					X	X	

Our implementation strategy will include first developing clinical protocols containing core components of the intervention to which fidelity is expected, along with aspects that may be adapted by local sites to aid implementation. In partnership with multidisciplinary teams at each site, we will adapt clinical practices from other contexts and available information about SL-BUP and XR-BUP to site-specific clinical protocols and implementation strategies. The study implementation facilitators will assist local champions to identify potential treatment providers and draw on existing resources for training and ongoing support.

Throughout the study timeline, we will use a participatory action research approach, adapted from the IF strategy in CTN-0069, to iteratively gather information from stakeholders and key informants to inform the planning and execution of actions to refine procedures and support implementation and enhance acceptability. This will be achieved by holding regular stakeholder meetings and conducting and repeating qualitative and quantitative assessments with clinical and administrative staff, patients, and other stakeholders. This IF will be guided by formative evaluation, an iterative process that uses quantitative and qualitative methods to tailor training, support, and overall implementation of the clinical protocol to each specific site. Formative evaluation will include site-specific organizational, provider, and patient factors potentially impacting uptake of provision of ED-initiated BUP to refine IF[26]. The quantitative components will include the Organizational Readiness to Change Assessment (ORCA) and change rulers; qualitative components will consist of qualitative interviews or focus groups with ED and community staff and providers, as well as ED patients and community stakeholders.

Given the urgency to provide generalizable information through this study to support OUD treatment where it is needed most, we will not delay introducing the clinical protocol to complete a formal pre-implementation formative evaluation. Rather, the formative evaluation began during development of this protocol, and will continue throughout the entire project. The goal of the formative evaluation is to gather information that will inform the effective implementation of a clinical protocol for OUD screening and ED- initiated BUP and as such, the process will be iterative and findings from both the quantitative and qualitative aspects of the IF will be used to optimize the clinical protocol, trainings, and resources as needed, and to make other adjustments as are indicated based on the formative evaluation. Eliminating a distinct pre-IF period will confound analyses of changes in readiness and preparedness (making it more difficult to demonstrate change); however, as neither screening for OUD nor BUP-initiation occurs in any of the proposed ED sites currently, eliminating a pre-IF period does not confound our ability to demonstrate change in adoption of the intervention.

Screening for OUD will be incorporated into standard clinical practice along with simple clinical documentation templates to improve detection, guide providers through intervention delivery, and improve quality of clinical data to assess process measures. This will support implementation and allow us to generate proportions for receipt of intervention components, including the primary outcome of initiation of BUP, and critical actions by health record review.

Patients identified and determined to be eligible for and willing to receive ED-initiated BUP will be contacted by research staff to participate in two research visits. The two patient-participant (see description below, Section 6.2) research visits will occur after written informed consent. The baseline research visit, assessing clinical care received during the index ED 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, assessing engagement in treatment on the 30th day after the index ED visit, amongst other secondary outcomes, will ideally occur no more than 7 days after this target, although outreach to reengage participants lost to contact may continue past this point.

This study will use mixed-methods with triangulation of qualitative and quantitative data from patient and staff perspectives along with health records to expeditiously and more comprehensively learn what is needed to sustainably introduce a clinical protocol for OUD screening, ED-initiated BUP, and referral for treatment in settings with high need, limited resources, and differing staffing structures.

5.2 Estimated Project Timeline

The highly compressed timeline reflects the urgency to initiate care and to expand strategies to address the opioid epidemic. The planned overall study period is 21 months, including pre-implementation assessment and preparation, study start up and recruitment, follow-up assessments, and data analysis and reporting.

Table 2: Estimated Project Timeline

	Study Month						
	1-3	**4-6**	**7-9**	**10-12**	**13-15**	**16-18**	**19-21**
Protocol and Team Development							
Assemble team/stakeholders							
Protocol development-version 1.0							
PRB Approval							
Regulatory approvals							
SAP, Data systems, eCRF development							
Hire, train site research teams							
Clinical Protocol Development, Implementation and CQI							
Implementation Facilitation							
Stakeholder-Participants: ED staff, Providers, Other Community and Patients							
Site surveys, needs assessment							
Qualitative interviews and focus groups							
ORCAs and Change Rulers							
Patient-Participants							
Recruitment							
Follow up							
Analysis and Reporting							
Data cleaning and data lock							
Data analysis							
Final study report and dissemination							

Patient-participant recruitment will begin once approvals are in place, clinical and research procedures are established, and staff are fully trained and ready. Patient-participant recruitment will take place over approximately 6 months. All patient-participants will complete a follow-up visit to assess engagement in treatment on the 30th day after the index ED visit.

The processes of assembling a team of champions and other stakeholders and learning about the site- specific resources and needs through weekly meetings and other implementation science-based activities is ongoing. Formal qualitative interviews, structured assessments, and focus groups will commence once approvals are in place and will continue throughout the study. Participatory action research involves generating a detailed account of the implementation facilitation process, including the cyclical process of interacting with stakeholders and patients to gather information and inform the planning and execution of actions to refining procedures and supporting implementation.

6.0 STUDY POPULATION

The study population includes 6 sub-samples.

1. ED STAFF: ED/Hospital leadership and staff: Leadership and staff across multiple disciplines (e.g., nurses, social workers, physicians, NPs, PAs, pharmacist, physician and nursing directors) at each ED site will be recruited to participate in the formative evaluation and the IF.
2. PROVIDERS: Community treatment providers/OTP leadership and program staff: Providers, leadership and staff involved in the provision of office-based BUP, community treatment, and/or at opioid treatment programs (OTPs) will be recruited to participate in the formative evaluation and the Implementation Facilitation.
3. COMMUNITY: Other Stakeholders: Other community leaders and members (e.g., EMS, fire department, police, local government leadership, community advocacy groups, etc.) may be recruited to participate in qualitative interviews or focus groups.
4. PATIENTS: ED patients will be recruited to participate in interviews or focus groups.
5. PATIENT-PARTICIPANTS: ED patients who are eligible for and willing to receive ED-initiated BUP will be recruited to participate in two research visits.
6. ALL ED PATIENTS: Administrative and health record data will be examined to assess rates of screening, assessment, eligibility determination, etc.

6.1 Stakeholder-Participant Eligibility Criteria

Inclusion Criteria:

1. A member of one of the stakeholder groups (1-4 above)
2. 18 years of age or older

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 60 stakeholders will participate in interviews or focus groups and approximately 150 will complete structured assessments.

6.2 Patient-Participant Eligibility Criteria

Inclusion Criteria:

1. 18 years of age or older
2. Eligible for and willing to receive ED-initiated BUP

Exclusion Criteria:

1. Not able to speak English sufficiently to understand study procedures and provide written informed consent
2. Unable or unwilling to provide written informed consent, sign a release of medical records or to participate in study procedures
3. Currently receiving any medication treatment for OUD at the time of index ED visit
4. Current research participant in a substance use intervention study or previous participation in the current study

5. Are 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
6. Inadequate locator information (unable to provide 2 unique means of contact)

Patients meeting all inclusion criteria and no exclusion criteria may be included as study patient-participants regardless of whether they receive or do not receive ED-initiated BUP.

We anticipate that approximately 120-180 patient-participants will be enrolled to be followed from the index-ED visit to the Day 30 follow-up, with a targeted minimum of 60 patient-participants.

7.0 STUDY SITES

The study will be conducted in three Emergency Departments:

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

Common to each site is the large proportion of economically disadvantaged or otherwise vulnerable patients served. Additionally, all sites have limited ED resources for managing a high need OUD patient population. Each hospital has differing ED staffing structures and outpatient OUD treatment referral options. None currently offer ED-initiated BUP.

7.1 Site Characteristics

Table 3: Site Characteristics

	Valley Regional Healthcare	Catholic Medical Center	Bellevue Hospital Center
Patient Volume	Low	Medium-High	Very High
Patient Need	High - high rates of OD; Fentanyl-only drug use common	High - high rates of OD; Fentanyl- only drug use common	High - high prevalence of psychiatric, medical co-morbidity
Setting	Rural	Urban with suburban and rural catchment zone	Urban
Institution	Private, critical access community hospital	Private, community hospital	Municipal, Academic-Affiliated, Tertiary Care Hospital and Level 1 Trauma Center
Referral options	Low	Medium	High
ED Physician Staffing	Single coverage, non-EM trained	Temporarily assigned, non- permanent staff	80 faculty members; 60 residents
ED Ancillary staffing	- No ED-based social work - No in-hospital addiction or psychiatric specialty coverage	- Permanent mid-level providers - Limited social work support	- Limited ancillary and support staff - Inadequate patient to nurse ratios (1:20) - Existing SBIRT and naloxone distribution programs
Space	Has space and ability to hold patients for extended periods	Lacks space and ability to hold patients for extended periods	Lacks space and ability to hold patients for extended periods
Unique Site Characteristics	Extremely limited community treatment options	Locum tenens staffing model poses training challenges	Expertise and partnerships to foster implementation and dissemination

Valley Regional Healthcare (VRH) is a low volume, critical access hospital located in rural New Hampshire serving Sullivan County, New Hampshire and Weathersfield Township, Vermont. VRH ED provides 24-hour single physician coverage with 2-3 nurses and/or paramedics support. The ED has approximately 10,000 annual visits and sees primarily white, non-Hispanic/Latino patients with Medicaid or other public health insurance. SL-BUP is on the hospital formulary but not currently available in the

ED. Sullivan County has limited resources for OUD patients, including few prescribers of medication treatment for OUD, no residential treatment programs, and no sober living facilities. Direct referrals to substance use treatment programs are not routinely made; instead patients are encouraged to search for programs independently.

Catholic Medical Center (CMC) is a moderately high-volume hospital located in Manchester New Hampshire, serving Hillsborough County. The ED has approximately 35,000 visits per year, seeing primarily white, non-Hispanic/Latino patients from the urban center and the adjacent suburban and rural catchment zones. The surrounding community of Hillsborough County has roughly one-third of New Hampshire's treatment programs, including approximately 18 buprenorphine providers and three OTPs[21]. SL-BUP is on the hospital formulary but not currently available in the ED. CMC recently changed to a locum tenens physician staffing model and, currently, has no ED physicians permanently on staff. This model, more common to rural areas due to regional physician shortages, relies on physicians temporarily assigned to a location for a period of several weeks or months. Among the unique challenges associated with this model includes difficulties identifying a local champion and repeatedly training new staff, a lack of familiarity with local resources, and potentially less of a sense of responsibility to address problems falling outside the scope of traditional emergency medicine care.

Bellevue Hospital Center is a high volume, tertiary municipal hospital and Level One Trauma Center in New York, New York serving an ethnically diverse patient population that is overwhelmingly of lower socioeconomic status. Bellevue has an average of 125,000 ED visits annually. The ED is staffed by 80 NYU School of Medicine faculty members and 60 residents, who work across multiple sites. When including clinicians and ancillary staff, the Bellevue ED operates with less than half the staff per patient than NYU Langone Medical Center ED and most other EDs. Having patient to nurse ratios exceeding 20:1 during busy shifts, and lacking 24-hour social workers, or at times, clerks to schedule appointments, differentiates this public hospital setting from other large urban EDs. SL-BUP is on the hospital formulary and can be ordered for single administration in the ED for patients already in formal addiction treatment. On-site, Bellevue Hospital has an inpatient detoxification center, an opioid replacement treatment clinic providing methadone and SL-BUP, a primary care-based SL-BUP clinic, and a non-medication treatment intensive outpatient program. Although Bellevue is rich in treatment programs and has a wealth of clinical expertise, the aforementioned limited resources and staffing for treating and connecting OUD patients with care serves as a barrier to accessing them. Further, the system for referring patients from the ED to outpatient addiction care is underdeveloped and support to help assume new responsibilities or coordinate care is limited. Currently, ED providers can only refer patients to outpatient addiction treatment programs by admitting patients to the inpatient detoxification unit. This restriction is in place, because of the lack of capacity of OUD treatment programs to accept new patients, the lack of ED staff to facilitate the referral, and the high proportion of non-adherence to appointments among patients referred from the ED. These characteristics align the Bellevue ED with the New Hampshire sites as settings with high need and limited resources to manage OUD in the ED.

7.2 Rationale for Site Selection

These sites enable assessment of feasibility, acceptability, sustainability and costs in heterogeneous settings including community, critical access and municipal EDs across rural to urban population densities with varying addiction treatment and research resources. This site diversity can inform a range of implementation strategies as it is expected that each site will contribute perspectives representative of EDs in various settings. This study complements CTN-0069 which is set in four resource-rich, academic, urban centers with established addiction resources and infrastructure. The three hospitals in the current study differ from one another. The New Hampshire facilities differ from the CTN-0069 sites in terms of community population density, ED patient volume, resources and infrastructure to support addiction treatment initiation and referral, clinical staffing models and clinical norms, electronic health record systems, and other known and unknown characteristics. Bellevue differs from the CTN-0069 sites insofar as it is a municipal hospital faced with different challenges and opportunities. As a public hospital, Bellevue has different institutional priorities and barriers unique to the extremely vulnerable

population it serves, as well as the challenges accessing and navigating care in an economically-strained and understaffed municipal healthcare system.

8.0 STUDY OUTCOMES

As a mixed-methods study, we will collect and converge both quantitative and qualitative data to develop an understanding of the feasibility, acceptability, and impact of introducing an ED clinical protocol for OUD screening, BUP treatment initiation, and referral for treatment.

8.1 Primary Outcome

The primary clinical outcome is the proportion of patients receiving ED-initiated BUP amongst patients who have been determined to be eligible for and willing to receive ED-initiated BUP. The primary outcome measure is receipt of ED-initiated BUP (binary) and will be abstracted from the health record.

Rationale: Our primary outcome is a measure of the success of introducing a clinical protocol for ED-initiated BUP in settings where there is currently none. 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. EDs do not provide definitive care for any chronic condition. Whether for uncontrolled or newly diagnosed diabetes, heart disease, or hypertension, patients are stabilized acutely, referred for definitive care, and provided a short-term prescription to bridge treatment until their follow-up visit when necessary. Yet, SUD is not addressed like other chronic conditions in the ED. 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. Almost universally, no components of Screening, Brief Intervention (whether brief advice, brief intervention, initiation of treatment), or Referral for Treatment (SBIRT) 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 180 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.

8.2 Secondary Outcomes

8.2.1 Main Secondary Outcome

The most important secondary outcome is the proportion of patient-participants who received ED-initiated BUP who are engaged in formal addiction treatment 30 days after the index ED visit. The measure will be patient-participant self-report of engagement in treatment, confirmed by the treatment provider (and is the same as the primary outcome of CTN-0069). Engagement in addiction treatment will be defined as enrollment and receiving formal addiction treatment on the 30th day after the index ED visit, assessed by direct contact with the facility and/or treating clinician. 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. These outcomes are exploratory.

8.2.2 Other Secondary Outcomes

Additional secondary outcomes of interest will be assessed, including, but not limited to those below. (See also Table 7 in Statistical Analysis, Section 12.)

1. Patient treatment:

- Self-reported days of use
- UDS results at 30 days post index ED visit
- Overdose events
- Healthcare utilization
- Quality of life
- Treatment satisfaction and acceptability

2. Clinical protocol:

- 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 eligible to receive ED-initiated BUP
  - Proportion eligible and willing to receive ED-initiated BUP
  - Proportion who received ED-initiated BUP (including formulation)
    - Number who needed multiple visits for induction
  - Proportion who received facilitated referral for treatment
  - 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
- Fidelity
  - Critical actions completed

3. Implementation barriers and facilitators

- Stakeholder acceptability over time (key informant interviews, focus groups)
- Stakeholder readiness/preparedness over time (ORCA, change rulers)
- ED staff, provider, community barriers and facilitators (key informant interviews, focus groups)
- Reasons for treatment choice
- Provider satisfaction

9.0 STUDY PROCEDURES

Study procedures are divided into (1) implementation facilitation; (2) clinical protocol, and (3) patient-participant activities.

9.1 Implementation Facilitation (IF)

A major goal of the current study is to determine whether an IF strategy increases the provision of ED-initiated BUP with referral for treatment and how to tailor strategies to different sites. Currently, none of the study sites offer ED-initiated BUP. Due to urgent public health need, IF activities will commence immediately and continue throughout the entirety of the study. We will measure the uptake of ED-initiated BUP over the study timeline, as described in Section 12.

9.1.1 Elements of Implementation Facilitation

IF will be based on a manualized program developed by Kirchner and colleagues[26] 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. As described below, PARiHS will be used to further explicate and design the IF, guide the ongoing formative evaluation, and revise the strategy in an iterative manner to improve implementation success. We will iteratively assess processes and receive feedback from providers, patients, and other stakeholders to amend and improve the feasibility, acceptability, and uptake of ED-initiated BUP in a way that is sustainable across the different sites. The individual components of IF are described below.

Formative Evaluation

Formative evaluation is a widely accepted implementation assessment approach designed to identify influences on the development, progress and effectiveness of implementation efforts[42]. As described above, we will use mixed-methods (qualitative and quantitative) to identify evidence, context, and facilitation-related factors impacting the provision of ED-initiated BUP with referral for treatment in the community and use these data to tailor, refine, monitor and evaluate the effectiveness of the IF. Change rulers and ORCAs will be used to gather evidence and context, related strengths and weaknesses in organizational readiness to implement BUP and referral, and to tailor the IF. Qualitative analysis will be used for planning, monitoring and evaluating activities from multiple perspectives (triangulation).

a. Implementation-focused formative evaluation will focus on the discrepancies between the implementation plan and its operationalization.

b. Progress-focused formative evaluation meetings will monitor achievement of implementation goals and performance targets to identify blocked progress, allowing steps to be taken to optimize the intervention.

c. Interpretive formative evaluation uses the data collected from the other formative evaluations and information collected at the end of the project regarding the participant experiences to clarify the meaning of successful or failed implementation and to enhance understanding of IF's impact. At the conclusion of the study, we will conduct an interpretive evaluation that will assess stakeholder views regarding (a) value of ED-initiated BUP with referral for treatment, (b) satisfaction or dissatisfaction with various aspects of IF, (c) reasons for ED-level action or inaction with respect to ED-initiated BUP with referral for treatment, (d) additional barriers and facilitators, and (e) recommendations for further refinements. Information will also assess stakeholders' beliefs regarding IF's success and overall ''worth''[42].

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 clinic-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.

Local Champions

We will identify local champions working clinically in the ED and community OUD treatment programs to help promote ED-initiated BUP with referral for treatment. 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. This information will be integrated into the formative evaluation.

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[26]. 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. Formative evaluation 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 share patient monitoring strategies. Training strategies will be based on adult learning theory and include 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).

Advising on ED-initiated BUP Clinical (Non-Research) Protocol Development

Serving in an advisory and consultant capacity, we will work with the clinical sites to help them develop a clinical protocol for ED-initiated BUP with facilitated referral tailored for their site. While informed and supported by research, these will be clinical guidelines, the contents of which and adherence to, will not be governed by this research. The induction and stabilization guidelines will contain a checklist of critical actions similar to those previously tested by D'Onofrio et al[15]. The goals of the protocol will be to simply and practically help providers identify candidates for ED-initiated BUP, perform pre-induction assessments, induce patients onto BUP in accordance with clinical prescribing guidelines specific to the formulation used (SL-BUP or XR-BUP, pending availability), and facilitate referral for treatment. The algorithm will provide guidance related to choice of formulation, dose, timing, and other decisions, including whether home induction with SL-BUP is appropriate. We will provide ongoing consultation to help monitor, support, and refine implementation. Adherence to the clinical protocol and, specifically the critical actions related to BUP induction, will be measured by the Clinical Protocol Adherence Log (described in Section 9.2.2.1).

Assistance with Facilitated Referrals

We will help sites identify OUD treatment providers for ongoing treatment for OUD, including a local champion to support the clinical intervention. We will assist in creating site-specific referral lists of medication treatment providers and other supportive resources for OUD patients. We may also help identify a practical approach to facilitating referrals.

Stakeholder Engagement

Stakeholder engagement will take place at the administrative, provider, community and patient levels. Efforts at increasing engagement will be informed by the focus groups and qualitative interviews and supported by the efforts of the local champions. This work will be informed by the Normalization Process Model[43] whereby we will work to have the screening, diagnosis and practices associated with OUDs

embedded into the everyday ED processes. Thus, normalizing the care into everyday real-world practice.

Tailoring the Program to Local Site

The IF strategy will be tailored to the local site informed by the formative evaluation and with feedback from local champions.

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 CQI and feedback practices. Once local CQI methods are established, sites will share CQI data with investigators to inform implementation and the refinement of site-specific clinical protocols. Sites will be provided aggregate feedback on eligible patients receiving BUP in the ED and referred patients' enrollment in ongoing treatment. Study facilitators will provide training booster sessions for sites with low implementation and those requesting such services.

Learning Collaborative

A Learning Collaborative will be formed by inviting each of the sites' local champions, and other key stakeholders, to participate in conference calls to promote shared learning regarding issues promoting and hindering implementation of addiction treatment. It will provide a dedicated time to discuss site-specific updates, challenges and possible solutions for implementation of addiction services. Detailed notes will be maintained; this information will be integrated into the formative evaluation. In addition, a listserv, similar to one established by Dr. Fiellin for the PCSS-buprenorphine[44] will be developed for use by all sites to support implementation through which at least one investigator experienced in OUD treatment with BUP will be on-call to provide clinical support.

9.1.2 IF - Informed Consent Procedures

Informed consent procedures differ based on the scope of study activities.

ORCA and Change Rulers Quantitative Assessments

An IRB approved verbal consent is embedded within the electronic surveys.

Focus Groups and Qualitative Interviews

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. Patient-participants 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 has been secured.

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

9.1.3 Data Collection as Part of Implementation Facilitation

Both qualitative and quantitative data will be collected as part of IF. Qualitative data will be from focus groups and individual qualitative interviews with ED staff and leadership, community OUD treatment providers, other community stakeholders and patients. Quantitative data from people representing these same groups (not necessarily the same people) will be in the form of ORCAs and Change Rulers.

9.1.3.1 Quantitative Data

Quantitative assessments for providers and staff, completed twice over the study period, will include ORCA and change rulers.

The ORCA[29] instrument is based on the PARiHS framework, and it is used to evaluate evidence, context and facilitation-related factors impacting implementation of ED-initiated BUP and referral for treatment. The PARiHS framework was first published in 1998 and refined in 2008(30-33). The recent revisited framework identifies four elements for determining successful implementation of an evidence-based practice into clinical care:

1. Nature of the innovation
2. Recipients of the facilitation, including people affected by and who influence implementation of the innovation
3. Qualities of the local and outer context in which the evidence is being introduced and enacted upon; and
4. Facilitation, the active process of promoting implementation by assessing and responding to the recipients and associated context

We will use change rulers, among appropriate providers and staff, to assess readiness and preparedness to provide ED-initiated BUP[28]. Baseline ORCA, and provider and staff readiness and preparedness scores will be used to determine evidence- and context-related strengths and weaknesses in organizational readiness to implement BUP and referral and to tailor the IF.

The ORCAs and Change Rulers will be administered electronically. An e-mail list of all ED administrators, providers and staff, as well as community treatment administrators, providers and staff will be generated for each site, and an individual invitation to complete these assessments will be e- mailed to each potential participant. Each respondent will also complete a brief Individual Characteristics survey that gathers information on clinical role, training, treatment of OUD and general demographic information. A select group of respondents will also complete a Site Characteristics survey gathering information on site staffing structure, patient demographics, and treatment of OUD at the site. Responses will be de-identified and confidentiality will be protected. Each individual will receive a unique ID to which all responses to the ORCA and Change Ruler will be tracked. Study staff will maintain a master list of potential participants and unique IDs to facilitate the distribution of participant incentives and the matching of follow-up responses to assessments.

Table 4: Schedule of Quantitative Assessments for Stakeholder-Participants

	Time-point	
Assessment	**Formative Evaluation**	**Study Close**
ORCA for ED Providers & Staff	**X**	**X**
ORCA for Community Providers & Staff	**X**	**X**
Readiness and Change Rulers for ED Providers & Staff	**X**	**X**
Readiness and Change Rulers for Community Providers & Staff	**X**	**X**

Organizational Readiness to Change Assessment (ORCA)

ED and community treatment providers and staff will complete the ORCA as part of the initial formative evaluation and again towards the end of the implementation period. The ORCA has been applied to the evaluation of interventions intended to promote evidence-based practices, including addiction treatment, and predicts implementation efforts[34-36]. This asks the respondent to rate local factors related to evidence, context, and facilitation on a 5-point Likert scale from strongly disagree to strongly agree. Facilitation questions will be omitted from the initial assessment if this part of the intervention has not taken place. We will use the same version of this assessment that was developed for CTN-0069, which is tailored to address issues related to ED-initiated BUP.

Change Rulers

Stage of change assessments have been validated and have been used in the field of addiction and mental health to assess readiness to adopt evidence-based treatments[37-40]. Change rulers will be completed as part of the initial formative evaluation and repeated over time. Change rulers for community treatment providers will assess individual readiness and preparedness to continue medication treatment for OUD for patients who have received ED-initiated BUP. Change rulers for ED providers will assess individual readiness and preparedness to provide ED-initiated BUP with referral for ongoing treatment for OUD. Change rulers for ED Staff/Administrators (non-prescribers) will assess ED readiness and preparedness to provide ED-initiated BUP with referral for ongoing treatment for OUD. “Preparedness” is defined as having the knowledge, ability and resources to provide the intervention (e.g., provider has received adequate training to prescribe BUP and has knowledge of an existing treatment program able to receive patients). “Readiness” is defined as willingness to provide the intervention (e.g., provider believes that medication treatment for OUD is a scientifically valid treatment for OUD). Change rulers utilize a scale of 1-10 to independently assess readiness and preparedness, where 1 equals “not (*ready; prepared*) at all” and 10 equals “totally (*ready; prepared*).”

9.1.3.2 Qualitative Data

At each of the study sites, we will conduct focus groups and/or individual qualitative interviews with a purposive sample of key stakeholders for the early formative evaluation and again 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[27].

9.1.3.3 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 and office-based BUP providers and representatives from OTPs and the community to allow for evaluation of processes from multiple perspectives (triangulation). A subset of key stakeholders may also be invited to participate in a focus group and/or interview to collect additional information related to implementation of the intervention.

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[27]. Focus groups will be conducted with approximately 4-8 study participants each[41].

For patients, we may use individual qualitative interviews due to timing of patient recruitment and scheduling logistics. For community stakeholders (e.g., EMS, fire department, police, local government leadership, community advocacy groups, etc.) we will primarily use individual qualitative interviews due to scheduling logistics.

9.1.3.4 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.

Conduct of Focus Groups/Interviews

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

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.

Stakeholder-Participant Incentives

Patients and providers will receive a $25 incentive for participating in a focus group or a one-on-one qualitative interview. Providers and staff will receive a $5 incentive for completion of the ORCA and a

$5 incentive for completion of the Change Ruler, for a combined total of $20, if both assessments are completed at both time points.

9.1.3.4 Data Analysis

See Section 12 for Statistical and Data Analysis.

9.2 Clinical Protocol

9.2.1 Clinical Protocol Development

Clinical protocols, specific to each site are currently in development at each site by teams including ED and hospital leadership and staff, members of the community where appropriate, and advisors with BUP and ED-initiated BUP expertise from the overall project team. Clinical protocols will address screening, assessment, eligibility determination, treatment and referral. In addition, during protocol development, training and other resource needs will be addressed as will integration with facilities' health records and methods for data capture. Plans will be developed for ongoing review as part of a CQI process, and for introduction in concert with the IF procedures described above.

9.2.1.1 Data Collection on Clinical Protocol Development

Qualitative data on clinical protocol development will be as above via the IF process.

9.2.2 Clinical Protocol Implementation

Once the clinical protocol is finalized and approved at the ED and/or hospital-level, necessary resources are in place and staff are fully trained, the clinical protocol will be fully implemented. Screening will begin, those screening positive will be further assessed, those deemed eligible for treatment will be offered BUP, and those willing to receive BUP will be treated in the ED and referred for continuing medication treatment for OUD in the community. Data on transition through this cascade (including on barriers) will be entered in the EMR (paper documentation may also be reviewed). The sample set will be the universe of patients coming through the ED during the implementation period.

9.2.1.2 Data Collection on Clinical Protocol Implementation

Qualitative data on clinical protocol implementation will be as above via the IF process. Quantitative data on the impact of clinical protocol implementation will be collected from the EMR and administrative datasets. We will request a 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 and site-specific internal CQI efforts. This dataset will provide the study primary outcome, i.e., the proportion of patients who receive ED-initiated BUP amongst patients who have been determined to be eligible for and willing to receive ED-initiated BUP.

<u>Clinical Protocol Adherence Log</u>

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)
- Baseline liver enzyme testing completed
- hcG obtained
- ED-initiated BUP provided (or offered and declined)
- BUP education and induction instructions provided
- Referral for treatment for OUD provided

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 Patient-Participant Outcomes

Patients who are eligible for and willing to receive ED-initiated BUP will be invited to provide written informed consent to participate in two research visits. 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 will ideally occur no more than 7 days after this target, although outreach to reengage participants lost to contact may continue past this point.

9.3.1 Research Procedures for Patient-Participants

9.3.1.1 Screening

Clinical screening for OUD will be implemented at each site via the clinical protocol. Study candidates will be patients who are determined to be eligible for and willing to receive ED-initiated BUP according to the clinical protocol established at each site (see patient-participant eligibility criteria, Section 6.2). Screening to assess/confirm study eligibility will be conducted by trained research staff during the index ED visit or ideally within 72 hours of ED discharge. Screening may be completed in person or by phone. 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.

9.3.1.2 Recruitment

Research staff may work rotating shifts in the ED, providing coverage on weekdays, evenings and weekends. All ED-initiated BUP eligible and willing patients will be notified that research staff may contact them to discuss participation in a research study either during their index ED visit or ideally within 72 hours of ED discharge. Patients will be given the opportunity to decline contact from research staff.

Research staff will learn of potential study candidates by (1) receiving direct referrals from ED staff; (2) review of the EMR and/or paper charts. Each site will establish procedures for documentation of ED-initiated BUP eligible and willing candidates and for timely communication to research staff. During each recruitment shift, research staff will generate a complete list of study candidates on a recruitment log. Research staff will review the log and, in the order that patients were identified to be potentially eligible, attempt to contact (in person, by phone or other means, depending on ED visit status) all ED-initiated BUP eligible patients who provided their permission to be contacted by research staff.

For patients who present to the ED during research staff shifts, study participation will be offered on site at the time of the index ED visit. For these individuals, study procedures, including verbal consent, eligibility, written consent and baseline assessments, will commence immediately. Candidates who present to the ED when there is no research staff coverage will be contacted and offered study participation as soon as possible following ED discharge. 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.

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. As our secondary (patient-participant-level) outcomes focus on recipients of ED-initiated BUP, we will employ a recruitment strategy that maintains a 2:1 ratio of patient-participants receiving ED-initiated BUP to patient-participants not

receiving ED-initiated BUP. Data from patient-participants in both groups will inform implementation barriers, facilitators, and acceptability. To maintain the aforementioned 2:1 ratio, patients who did not receive ED-initiated BUP and who are eligible for research participation will be enrolled purposively with a limit of enrollees established based on the relative number of participants in each group.

9.3.1.3 Informed Consent

Before performing any study assessments, research staff will request the patient's verbal consent to assess eligibility using an IRB-approved verbal consent script. After the patient has provided verbal (not signed) consent, research staff will collect basic demographics information and confirm that the candidate meets all the inclusion criteria and none of the exclusion criteria. If the candidate meets all the eligibility criteria on the Eligibility Checklist, s/he will be offered participation. Candidates meeting inclusion criteria who are excluded or who refuse to participate, as well as their reasons for exclusion or nonparticipation, will be documented.

All candidates remaining eligible following this screening will be asked to provide written consent to participate using the IRB-approved informed consent document. Prior to documenting written informed consent, research staff will explain the study to the potential patient-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.

The IRB of record has approved the use of a compound authorization form that serves as a combined consent and HIPAA disclosure form allowing study access to protected health information 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.

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 will receive 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.

9.3.1.4 Eligibility Confirmation and Enrollment

Once eligibility is confirmed, and both written informed consent and release of medical records is obtained, 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 study will be considered screen failures.

9.3.1.5 Baseline Procedures

Baseline procedures will continue with structured assessments on quality of life, drug use, and healthcare utilization. See Table 5 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.

9.3.1.6 Intervention

This is not an intervention study, but rather a study of interventions introduced as part of routine clinical care.

9.3.1.7 Referral Procedures

Study participants may receive a facilitated referral for ongoing medication treatment for OUD or other addiction treatment as part of clinical care, informed by site-specific clinical guidelines.

9.3.1.8 Follow-up Visit (Day 30)

The follow-up research visit will assess engagement in treatment on the 30th day after the index ED visit. At the follow-up visit, patient-participants will be asked to provide a urine sample and complete specified research assessments (See Table 5: Schedule of Assessments for Patient-Participants).

9.3.1.9 Patient-Participant Retention

Rigorous retention strategies will be employed to maintain contact with patient-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.

9.3.1.10 Patient-Participant Withdrawal

Premature Withdrawal of Patient-Participants: All patient-participants will be followed for the duration of the study unless they withdraw consent, die, or the investigator or sponsor decides to discontinue their enrollment for any reason. Reasons for the investigator or sponsor terminating a participant from the study may include, but are not limited to, the participant becoming a threat to self or others, lack of funding, or DSMB early termination of the study for safety or effectiveness reasons.

9.3.1.11 Patient-Participant Reimbursement

Patient-participants will be compensated for their participation in the study. Patient-participants will receive $75 for completion of screening and baseline and $100 for the Day 30 follow-up visit.

9.3.1.12 Research Assessments for Patient-Participants

Table 5: Schedule of Research Assessments for Patient-Participants

Assessment	Screening	Baseline	Day 30
ELIGIBILITY AND ENROLLMENT			
Verbal Consent	X		
Prisoner Status Assessment	X		
Demographics	X		
Eligibility Summary	X		
Enrollment (Inclusion/Exclusion)	X		
GENERAL			
Written Informed Consent and Medical Release	X		
Additional Demographics		X	
Locator Information Form		X	X
DSM-5		X	
Other Substance Use		X	
EuroQol-5 Dimensions (EQ-5D)		X	X
Motivations, Attitudes and Expectations		X	
Study Completion			X
HEALTH SERVICES			
Inpatient Utilization		X	X

Assessment	Screening	Baseline	Day 30
Outpatient Utilization		X	X
Health Status		X	X
Healthcare Visit Logistics		X	
ED Visit Review		X	
ED Visits and Hospitalizations			X
PROCESS OUTCOMES			
Engagement in Treatment			X
Prescription Drug Monitoring			X
Treatment Decision		X	
Treatment Satisfaction/Acceptability			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

9.3.1.12.1 General Measures

Demographics and Additional Characteristics: The demographics form collects information about demographic characteristics of the study candidate, including age, gender, cultural/ethnic group, educational level, marital status, and type of insurance. The demographics form will be completed once for study candidates at screening and an additional demographics form is completed once at baseline for study patient-participants.

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. Candidates meeting prisoner status at screening will not be enrolled.

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 at the Day 30 follow-up. Data entered in this form will be encrypted and will not be used in data analyses.

EuroQol-5 Dimensions (EQ-5D): The EuroQol is a structured interview that collects general health information applicable to a wide range of health conditions and treatment, providing a simple descriptive profile and a single index value for health status. The EQ-5D is collected at baseline and at the Day 30 follow-up visit.

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

Study Completion: This form tracks the patient-participant's status in the study. It is completed at the participant's 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.

Inclusion/Exclusion and Eligibility Summary: These forms collect information regarding patient- participant eligibility. The Participant Eligibility form documents eligibility criteria collected during screening and prior to written informed consent. After written informed consent is obtained, inclusion and exclusion criteria are assessed and documented on the Inclusion/Exclusion Checklist and Enrollment form. Only participants who continue to meet study eligibility criteria are allowed to continue with the screening process, and enrollment.

9.3.1.12.2 Measures of Primary and Secondary Clinical Outcome

Engagement in Treatment Survey: At the Day 30 follow-up visit patient-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: Residential/Inpatient Treatment; Level IV: Medically managed intensive inpatient treatment or Other-specified. ED visit is considered Day 0; Engagement is assessed on Day 30.

Prescription Drug Monitoring Program: The States' Prescription Drug Monitoring Programs will be accessed to identify all opioid prescriptions that patient-participants fill during the follow-up period. This form will be completed once at the Day 30 visit.

Overdose Events and Risk Factors: We will ask patient-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. In addition, research staff may review the EMR, EMS records (pending availability), and, when appropriate (missing participant), medical examiner records.

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.

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

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.

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.

Treatment Decision: This form will collect information on the decision to receive BUP, choice of formulation and other factors impacting patient choice. This form will be completed once at baseline.

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

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 patient-participant input.

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 patient-participant input.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5): The DSM-5 criteria are assessed during the baseline visit to determine a current diagnosis of moderate-to-severe opioid use disorder. This assessment will be completed electronically and will be automatically scored. The score will not influence study eligibility criteria.

9.3.1.12.3 Safety Events

Opioid non-fatal overdose events, healthcare utilization including ED visits and hospitalizations, and all deaths including fatal overdoses will be tracked within the 30 days between the index ED visit and Day

30. Study staff are obligated to continue to follow-up on identified safety events until the close of the Day 30 visit window. Overdose events since enrollment will be captured by patient-participant self-report, potentially collateral report (e.g., family), review of health records and EMS records (pending availability). In the event of drop-out, we will 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 patient-participant family and friends, ED visits, etc.). 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. If during the development of clinical protocols, additional concerns arise, facility SOPs will be updated.

9.3.1.12.4 Drug Use Measures

Urine Drug Screen: Urine testing will be performed for the presence of the following drugs: opioids, oxycodone, 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. Urine testing supplies will be provided to the sites.

Timeline Follow-Back (TLFB): The Timeline Follow-Back[24] procedure will be used to elicit the patient-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.

10.0 MEDICATION

As part of the clinical protocol, SL-BUP and/or XR-BUP will be included in the hospital formularies and administered per the clinical protocol.

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 Informed Consent 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. Clinical training for ED and community treatment providers and staff are detailed in Section 9.

12.0 STATISTICAL ANALYSES

Using a participatory action research approach and mixed methods, we will develop, introduce, and iteratively update site-specific ED clinical protocols and implementation plans for OUD screening, treatment, and referral to optimize feasibility and acceptability. Barriers and facilitators to implementation will be explored and impact of remediation efforts and iterative process changes will be assessed through sequential qualitative and quantitative inquiry and feedback generated through the learning collaborative. Converging provider and patient perspectives with process measures and intervention outcomes, including proportions screened, treated, and remaining engaged in treatment, will provide explanation to contextualize and better understand feasibility, acceptability, and patient-level outcomes.

12.1 Primary Outcome

Aim 2 of CTN-0079 is described as, over the course of the study and as XR-BUP is added to hospital formularies, to estimate the percentages and confidence intervals of patients assessed, treated and engaged in treatment at day 30. We have defined the primary outcome from Aim 2 as the probability of an individual receiving ED-initiated BUP given that the individual is determined to be eligible for and willing to receive ED-initiated BUP. We refer to this below as the implementation probability. In our original study plan, we assumed that 120-180 individuals (ED patients), identified evenly from 3 sites, will be available with which to investigate this primary outcome. Subsequently, we now anticipate a larger number of patients will be identified as willing and eligible to receive ED-initiated BUP, and thus the number of ED patients who enroll and become study patient-participants should also increase (Section 12.3). These increases would likely only increase precision, we have not amended the original statistical analytic plan with these updated numbers – described hereafter.

Implementation probabilities are conditional

This simple definition is complicated by the fact that, at the beginning of the trial, only SL-BUP will be available. At some as-yet unknown time point, XR-BUP will also become available. This means that there are two implementation probabilities, p_{early}, when only SL-BUP is available, and p_{late}, when both SL and XR are available at every site. There is no prior reason to believe $p_{early} = p_{late}$. We face the question of whether to decompose p_{late} into p_{SL} and p_{XR}. With respect to the latter question, consider a patient who, having been offered both SL and XR, opts for XR. Should this be counted as a vote against SL? The patient might have chosen SL if that were the only choice on offer. It is better to speak of these implementation probabilities as conditional: p_{early} = Pr(choose SL|only SL available), for which we can use the shorthand Pr(SL|SL). There are also Pr(SL|SL & XR) and Pr(XR|SL & XR), but we cannot

estimate Pr(XR|XR), since there will be no period during which only XR is available. From the public-health point of view, Pr(SL|SL & XR) and Pr(XR|SL & XR) are less important than p_{late}=Pr(SL or XR| SL & XR), since, when XR becomes available, it will always be on offer along with SL, and the main question in this trial is whether the individual would be willing to receive ED-initiated BUP . To summarize, the most important estimands are p_{early} = Pr(SL|SL) and p_{late}=Pr(SL or XR|SL & XR).

A partly Bayesian approach

To avoid difficulties with zero counts, we use Bayesian estimates for the site-level p_{early} and p_{late} values, assuming beta likelihoods uniform priors to derive posterior moments. That is, if there are S successes and F failures for a site at a particular (before/after) time, we take the implementation probability estimate for that site-time 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 p_{early} estimate to be the average of the three site-level estimates. Because the site-level p_{early} estimates are independent, the variance of the overall p_{early} 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 $\pm 1.96 * \sqrt{V_{early,overall}}$. An exception to this is that we did not allow confidence limits to stray outside (0,1).

Similar statements are true of the p_{late} estimates.

SAS code

SAS code to perform this calculation is below. We assume the results of the trial are in file RESULTS, where there is one record per patient, with variables Y, site, and indic, 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
- indic = 1 if the patient was recruited after XR-BUP became available, and 0 if the patient was recruited before XR-BUP became available.

The outcome of the calculations is in file EST, where:

- (e10, e11) are the site-specific estimates of the implementation probabilities for the BEFORE and AFTER periods
- (e20, e21), and (e30, e31) are the corresponding site-specific implementation probabilities for sites 2 and 3, respectively
- (v10, v11), (v20, v21), and (v30, v31) are the estimated variances for (e10, e11), (e20, e21), and (e30, e31)
- (pearly, plate) are the estimated implementation probabilities for the early and late periods
- (earlylcl, earlyucl, latelcl, lateucl) are the corresponding 2-tailed 95% confidence limits

```
proc summary nway data = results;
  class site indic;
  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));
  siteindic = 10*site + indic;
  keep siteindic heads tails e v;
  run;

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

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

```
data est;
  merge tsumme tsummv;
  /* intentional merge without BY statement */ drop _name_;
  pearly = (e10 + e20 + e30)/3;
  plate = (e11 + e21 + e31)/3;
  vearly = 1/9 * (v10 + v20 + v30);
  vlate = 1/9 * (v11 + v21 + v31);
  earlylcl = min(1, max(0, pearly - 1.96 * sqrt(vearly)));
  earlyucl = max(0, min(1, pearly + 1.96 * sqrt(vearly)));
  latelcl = min(1, max(0, plate - 1.96 * sqrt(vlate)));
  lateucl = max(0, min(1, plate + 1.96 * sqrt(vlate)));
  run;
```

Description of simulation

In the simulations reported below, we investigate bias and the 90th percentile of the distribution of the 95% confidence interval width for p_{early} and p_{late} that result from different combinations of true values of p_{early}, p_{late}. We also introduce variability among sites via the parameter Δ, as reported in Table 6. When $\Delta = 0$, there is no variability between sites, while the difference between the site-level p_{early} values is very large when $\Delta = 3$. A similar statement is true for site-level p_{late} values. To assess the impact of Δ on site-level variability, see Appendix B. When there is site-level variability, the p_{early} and p_{late} values we estimate here are the unweighted averages of the site-level probabilities.

Table 6: Simulation parameters generating scenarios

$(p_{early}, p_{late}) = (0.1,0.3,0.7,0.9)$ such that $p_{early} \leq p_{late}$ Δ

$= (0,0.1,1,2,3)$

In our simulation, we assumed that 180 individuals from three sites were identified over a 6-month period and contribute to the calculation of the primary outcome measure. And that an individual is considered "identified" when they have an ED visit for which they were found (via EMR abstraction) to be eligible and willing to receive ED-initiated BUP.

We call each combination of simulation parameters a scenario. There are thus 4*5=20 scenarios. Each scenario was based on 10,000 iterations, and gave rise to four results: a mean bias and a 90th percentile of the width of the 95% confidence interval for each of (p_{early}, p_{late}). Each scenario assumed 180 individuals were identified via the EMR and that sites recruited at the same rate. The date at which XR became available was uniformly distributed over the 6-month period, with each patient being assigned to a site-level p_{early} or p_{late} according to whether the patient was identified before or after the XR-date. We assumed the XR-date was the same at all the sites.

Simulation Results

The simulation results presented here are for the assumption that 180 patients will be available with which to investigate the primary outcome (i.e., "identified"). Simulation results for other sample sizes may be presented in the statistical analysis plan (SAP).

We display the results of this simulation in Figures 1-4.

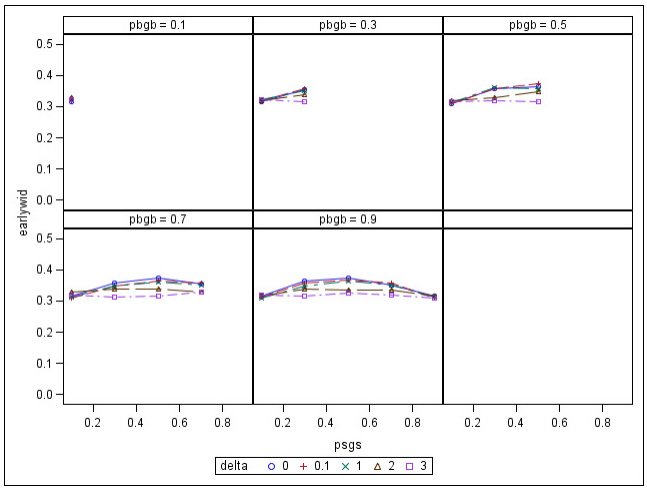

Figure 1: 90th percentiles for the 95% confidence interval width of the estimate of p_{early} as a function of the true value of p_{early}, with different lines in a panel representing different values of Δ. Panels show results for different values of p_{late}. Note that the vertical scale for each panel is (0, 0.5).

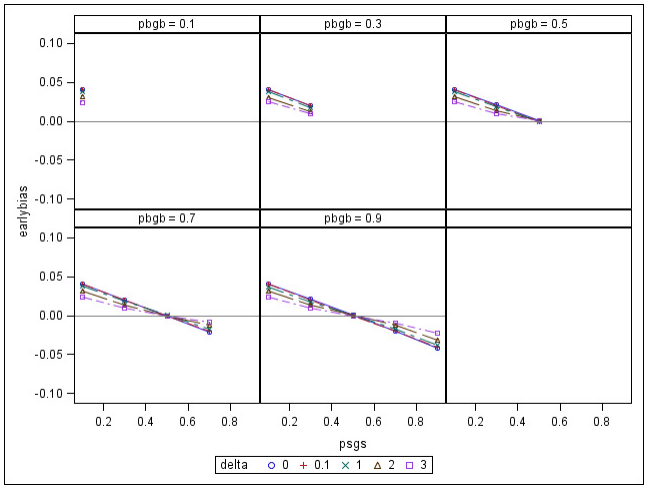

Figure 2: Mean bias for p_{early} as a function of the true value of p_{early}, with different lines in a panel representing different values of Δ. Panels show results for different values of p_{late}. Note that the vertical scale for each panel is (-0.1, 0.1).

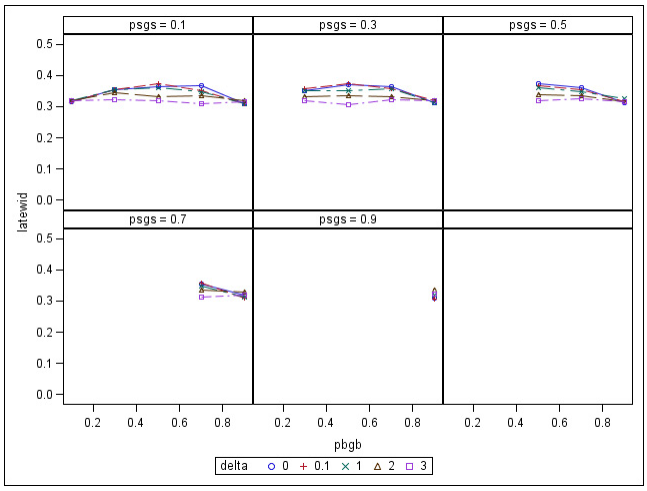

Figure 3: 90th percentiles for the 95% confidence interval width of the estimate of p_{late} as a function of the true value of p_{late}, with different lines in a panel representing different values of Δ. Panels show results for different values of p_{early}. Note that the vertical scale for each panel is (0, 0.5).

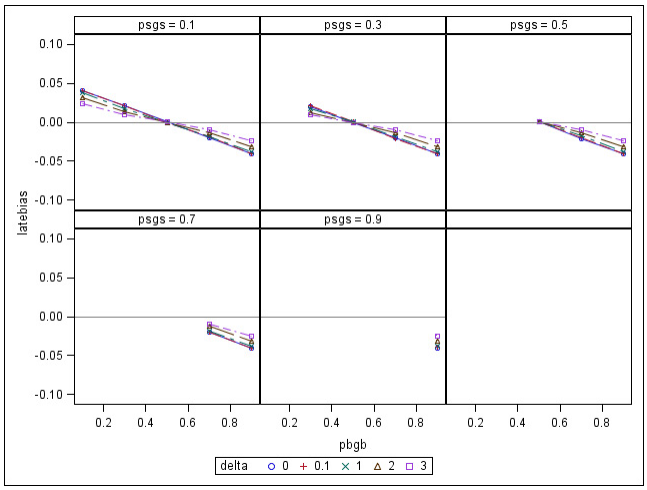

Figure 4: Mean bias for p_{late} as a function of the true value of p_{late}, with different lines in a panel representing different values of Δ. Panels show results for different values of p_{early}. Note that the vertical scale for each panel is (-0. 1, 0.1).

Summary

- There is minor upward bias for small true probabilities, and minor downward bias for large ones, but bias is not large for most parameters investigated in this simulation.
- It is unlikely that we will see confidence intervals wider than 0.4 in this trial.

12.2 Secondary Outcomes

Table 7 describes various probabilities of secondary outcomes of interest emanating from Aim 2. We will investigate these by methods similar to those developed above for the primary outcome. Administrative data and electronic medical record (EMR) data should be available and allow us to estimate proportions to assess patient-level outcomes. We will also assess differences between sites and the slope of change in proportions over time from since clinical protocol implementation.

Table 7: Secondary Outcomes: Proportions of Interest

	Numerator	Source Population	Denominator
1	Opioid Screen completed	All ED patients	ED patients (adult)
2	Opioid Screen positive	All ED patients	Screen completed
3	ED-initiated BUP eligibility assessment completed	All ED patients	Opioid Screen positive
4	ED-initiated BUP eligible	All ED patients	Opioid Screen positive
5	ED-initiated BUP eligible and willing	All ED patients	ED-initiated BUP eligible
6	**ED-initiated BUP received (primary outcome)**	All ED patients	ED-initiated BUP eligible and willing
7	Initial contact with medication provider (9-day)	Patient-participants	ED-initiated BUP received
8	**Engaged in formal addiction treatment on the 30th day post-ED visit (most important secondary outcome)**	Patient-participants	ED-initiated BUP received
8a	Engaged in formal addiction treatment on the 30th day post-ED visit (most important secondary outcome)	Patient-participants	ED-initiated BUP eligible and willing but not receiving ED-initiated BUP
9	Received a facilitated referral for treatment	All ED patients	ED-initiated BUP received
9a	Received a facilitated referral for treatment	All ED patients	ED-initiated BUP eligible and willing but not receiving ED-initiated BUP
10	Received XR-BUP (in ED)	All ED patients	Received any BUP (in ED)

The primary outcome (#6) and outcome #8, the most important secondary outcome, i.e., the probability of being engaged in formal addiction treatment at day 30, given that any BUP has been received in the ED, are both emboldened in Table 7. We expect to have a sample of at least 42-60 patient-participants with which to assess outcome #8.

In addition, analyses will be performed for each secondary outcome listed in Section 8.2.1, including self-reported days of opioid use (pre-post comparison using 7-day Timeline Followback), UDS results at Day 30 post index ED visit, overdose events, healthcare utilization, quality of life, treatment satisfaction and acceptability among the patient-participants. Fidelity to critical actions related to BUP induction as measured by the Clinical Protocol Adherence Log (Section 9.2.2.1) will be assessed. Initial and changes in readiness and preparedness scores (ORCA, readiness and preparedness rulers) will be reported as well.

12.3 Recruitment and Enrollment

For our original statistical plan, we calculated the precision for the study assuming 180 ED patients would be identified as willing and eligible to receive ED-initiated BUP in accordance with site-specific clinical protocols (i.e., the population making up the denominator for the primary outcome). As described below, we estimated that of those patients a total of 90 will be enrolled as study patient-participants consisting of two subgroups: (i) 60 patients who receive BUP (this group is the denominator of outcome #8) and (ii) 30 patients who do not receive BUP. According to our recruitment strategy, we will preferentially enroll patient-participants who receive BUP to those who do not receive BUP (approximately 2:1). Subsequently, we now anticipate enrolling a larger number of patient-participants perhaps 120 (80 who receive BUP and 40 who do not receive BUP) or possibly 180 total patient- participants. If 120-180 patient-participants are enrolled, we estimate that the number of individuals identified as willing and eligible for ED-initiated BUP (i.e., primary outcome denominator) is 240-360.

12.3.1 BUP

The original statistical plan, described hereafter, assumed that 120-180 individuals (ED patients identified as willing and eligible to receive ED-initiated BUP), identified at a constant rate and evenly from 3

sites, will become available over the anticipated 6-month recruitment period to investigate the primary implementation probability outcome. Of those patients, we expect that only 42-60 patients receiving ED-initiated BUP will be available for the secondary Day 30 treatment engagement outcome. (i.e., we estimate 40% of the 120-180 patients identified will receive ED-initiated BUP, and that 82.5% of these patients will consent to be followed). We also assume that another month will be necessary after 6 months, to collect outstanding treatment engagement outcomes.

Assuming 180 patients, the time each patient-participant is followed for these two outcomes is displayed pictorially in Figure 5, where the blue solid line indicates recruitment for the primary implementation probability outcome, the red dashed line indicates recruitment for the secondary Day 30 treatment engagement outcome, and the green dot-dash line indicates the end of follow-up for treatment engagement. The experience of an individual patient-participant is given by an (imaginary) horizontal line segment that extends from the participant's enrollment (blue solid line) to the end of the engagement follow-up (green dot-dash).

We expect it to take about a month to identify about 30 ED patients who are eligible for and willing to receive ED-initiated BUP. So, the slope of the blue line is 180/6=30 patients per month. But we feel it likely that the probability of receiving ED-initiated BUP for such an individual is only about 72/180=0.4, so that, of the 30 patients identified in a month, only about 30*0.4=12 will actually have received ED-initiated BUP, and further, that the majority of those (82.5%) will consent to be followed (0.4*0.825 = 0.33), so that 30*0.33=10 individuals per month will thus become patient-participants and part of the Day 30 engagement denominator. This means that the slope of the red dashed line is 60/6=10 patient-participants per month. Because we count loss to follow-up after receiving ED-initiated BUP as a failure with respect to engagement, there are effectively no missing values for 30-day treatment engagement, which is why the green dot-dash line is parallel to the red dash line but shifted 30 days to the right. After 6 Months, there is a 30-day (plus one-week window) wait until the remaining engagement outcomes are collected.

This graph demonstrates how the sample size available for the Day 30 treatment engagement outcome depends on the probability.

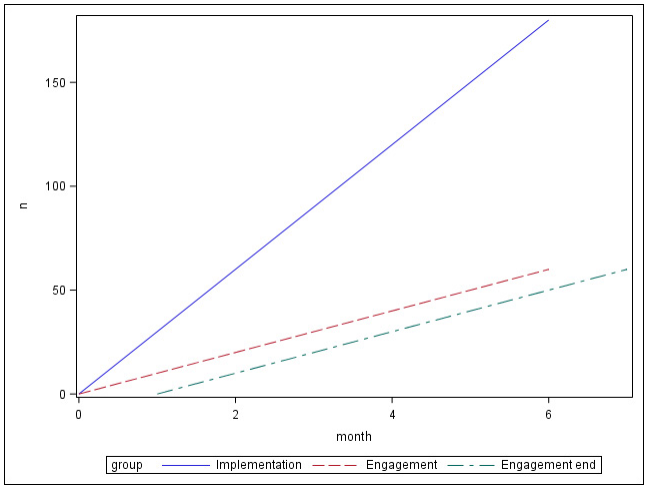

Figure 5: Enrollment for ED-initiated BUP (primary implementation probability outcome) and 30-day engagement in treatment in CTN-0079

The expected cumulative numbers of individuals being assessed for certain milestones is given in Table 8, assuming 180 individuals will be identified and found both eligible for and willing to receive ED-initiated BUP.

Table 8: Expected cumulative numbers of individuals capable of being assessed for selected study milestones outcomes, by month

Month	Primary Implementation Probability Outcome	Treatment Engagement Denominator	Treatment Engagement Numerator
	n=180	**n=180**	**n=180**
1	30	10	0
2	60	20	10
3	90	30	20
4	120	40	30
5	150	50	40
6	180	60	50
7-8			60

12.4 Missing Data

There will be no loss to follow-up for the implementation probability primary outcome, because it is assessed almost immediately on ascertaining that the individual is eligible for and willing to receive ED-initiated BUP.

With respect to the secondary Day 30 treatment engagement proportion, patient-participants lost to follow-up after receiving ED--BUP will be counted as not engaged in treatment for outcome #8, thus will contribute to both numerator and denominator instead of generating missing data. Accordingly, we ignore the possibility of loss to follow-up in the treatment engagement power calculations.

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. In our previous research, we developed patient tracking and communication protocols that resulted in very low rates of missing data. These field-tested procedures with proven effectiveness, with the necessary site-specific adjustments, will be disseminated across all study sites.

12.5 Controlling Type 1 Error in Secondary Analyses

CTN-0079 is a non-randomized brief study in which formal and rigorous hypothesis-testing will not be carried out. Because of this, we do not anticipate multiple-comparison adjustments when performing secondary analyses, but instead will be mindful of the multiple testing problem, thus report secondary findings as noteworthy hypothesis-generating results only when their p-values are considerably smaller than 0.05.

12.6 Interim Monitoring

No interim looks at primary or secondary outcomes are planned for this brief study.

12.7 Safety Outcomes

Opioid non-fatal overdose events, healthcare utilization including ED visits and hospitalizations, and all deaths including fatal overdoses will be tracked within the 30 days between the index ED visit and Day 30.

12.8 Exploratory Analyses

We will evaluate a limited set of patient, ED, and provider characteristics for their potential effect on the primary outcomes including:

- ED characteristics

- Provider characteristics
- Patient-participant characteristics

We will use appropriate non-parametric, parametric, and analysis of variance statistical procedures to descriptively evaluate the key characteristics of each study site and to evaluate comparability of baseline characteristics among patient cohorts enrolled at each of the study sites and overall during the study.

12.9 Process Outcomes

The process aims described in Protocol Section 8.2.2 are intended to describe screening, enrollment, medication administration, and navigation to ongoing medication treatment for OUD and/or other formal addiction treatment. For each of these aims, only descriptive statistics will be performed, including proportions for categorical data and means, standard deviations, minimum, and maximum for continuous variables. No inferential statistics will be performed on the process outcomes.

12.10 Qualitative Statistical Analyses

We will utilize the Rapid Assessment Process[41] 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 8-10 events, either by focus group or individual interview, will occur until themes begin to repeat. This process allows for results to be used for planning, monitoring and evaluating activities when prolonged fieldwork usually associated with traditional qualitative research is not possible. Recognizing our aggressive time schedule, we will plan to schedule focus groups and interviews early so that we are ready to conduct them as soon as possible after IRB approval.

Using directed content analysis[45], 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 patient-participant assessments and provider/organizational readiness and preparedness assessments.

13.0 REGULATORY COMPLIANCE AND SAFETY

13.1 Statement of Compliance

This study will be conducted in compliance with the current version of the protocol, in full conformity with the ethical principles outlined in the Declaration of Helsinki, the Regulations for the Protection of Human Subjects codified in the International Council for Harmonization Good Clinical Practice (GCP) Guidelines, and all other applicable regulatory requirements. Participating sites must obtain written approval of the study protocol, consent forms, other supporting documents, recruitment materials, and any other materials given to the participant from the Institutional Review Board (IRB) of record to participate in the study. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate Ethics Review Committee (ERC) or IRB. Any amendments to the protocol or consent materials must be approved before they are implemented. Unanticipated problems involving risk to study participants will be promptly reported to and reviewed by the IRB of record, according to its usual procedures.

13.2 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 will agree to rely on BRANY and will enter into reliance/authorization agreements for Protocol CTN-0079. BRANY 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, site investigators will obtain written IRB approval from BRANY to conduct the study. If changes to the study protocol become necessary, protocol amendments will be submitted in writing by the Lead Node for IRB approval prior to implementation. In addition, the IRB will approve all consent forms, recruitment materials, social media use and any materials given to the participant, and any changes made to these documents throughout study implementation. For changes to the consent form, a decision will be made regarding whether previously consented participants need to be re-consented. IRB continuing review will be performed annually, or at a greater frequency contingent upon the complexity and risk of the study. Each site principal investigator (PI) 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 Lead Investigators prior to the initiation of research activities at the site and must be available at any time for audit.

13.3 Informed Consent

The informed consent process is a means of providing study information to each candidate 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 patient-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 single/central IRB. To confirm that each consent form contains the required elements of informed consent as delineated in 21 CFR 50.25(a) and CFR 46.116(a), as well as pertinent additional elements detailed in 21 CFR 50.25(b) and 45 CFR 46.116(b), a copy of the IRB-approved consent, along with the IRB study approval, must be sent to the Clinical Coordinating Center (CCC) and the Lead Node (LN) prior to the site initiation visit and with each subsequent consent revision. Every patient-participant is required to sign a valid, IRB-approved current version of the study informed consent form prior to the initiation of any study related procedures. The site must maintain the original signed informed consent for every participant in a locked, secure location that is in compliance with all applicable IRB and institutional policies and that is accessible to the study monitors. Every focus group and qualitative

interview participant will verbally consent to participation. Each participating site will request a Waiver of Documentation of consent.

Each participating site will request a Waiver of Informed Consent/HIPAA authorization for the abstraction of data from the medical record.

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 Good Clinical Practice (GCP) and Human Subjects Protection (HSP) training, as mandated by NIDA standard operating procedures.

13.4 Quality Assurance and Safety Monitoring

13.4.1 Confidentiality

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

To further protect the privacy of study participants, the study is covered by a federal Certificate of Confidentiality (CoC) from NIH which protects identifiable research information from forced disclosure. This protects participants against disclosure of sensitive information (e.g., drug use). The CoC allows the investigator and others who have access to research records to permanently refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level, excepting certain circumstances. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, a Certificate of Confidentiality helps achieve the research objectives and promotes participation in studies by helping assure confidentiality and privacy to participants.

Participant records will be held confidential, using 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.

13.4.2 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 single/central IRB of record and obtaining the appropriate approvals or waivers to be in regulatory compliance. Releases of participant identifying information that are permitted by the HIPAA regulations, but which are prohibited by other applicable federal regulations and/or state/Commonwealth law and regulation, are prohibited.

13.5 Investigator Assurances

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

13.5.1 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. Investigators will confirm to the sponsor annually that they have met their institutional financial disclosure requirements. It is the responsibility of the investigator to maintain appropriate disclosure to their individual institution according to their requirements.

13.6 Clinical Monitoring

The monitoring of the study sites will be conducted on a regular basis using a combination of NIDA-contracted monitors and local node site managers. Investigators will host periodic visits by NIDA-contracted monitors and local node site managers. The purpose of these visits is to encourage and assess compliance with GCP requirements and to document the integrity of the trial progress.

NIDA-contracted monitors 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, 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 and NIDA CCTN.

Qualified Node QA monitors or other designated party(ies) may provide site management for each site during the trial. Node QA managers 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 managers will verify that study procedures are properly followed and that site personnel are trained and able to conduct the protocol appropriately. If the Node manager's review of study documentation indicates that additional training of site study personnel is needed, Node staff 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.

13.7 Special Populations to Consider

13.7.1 Inclusion of Women and Minorities

The study is open to any gender, race or ethnicity.

13.7.2 Prisoners

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

If a participant becomes incarcerated during the study, follow-up procedures may be continued in accordance with IRB approvals. Procedures must be compliant with 45 CFR 46 Subpart C. 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 single IRB. 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.

13.7.3 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.

13.8 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 research site for regulatory document compliance prior to study initiation, throughout the study, as well as at study closure.

13.9 Records Retention and Requirements

Research records for all study participants (e.g., case report forms, source documents, signed consent forms and releases, transcriptions, and regulatory files) are to be maintained by the investigator in a secure location for a minimum of 3 years after the study is completed and closed. These records are also to be maintained in compliance with IRB, state and federal requirements, whichever is longest. The sponsor and Lead Investigator must be notified in writing and acknowledgment must be received by the site prior to the destruction or relocation of research records.

13.10 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 described in Section 13.14.2 At the completion of the trial, the Lead Investigator will provide a final report to the Sponsor.

13.11 Audits

The Sponsor has an obligation to ensure that this trial is conducted according to good research practice guidelines and may perform quality assurance audits for protocol compliance. The Lead Investigator and authorized staff from the 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 (DHHS), 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.

13.12 Study Documentation

Each participating site will maintain appropriate study documentation (including medical and research records) for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. Study documentation includes all CRFs, 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 9.1.3, 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.

13.13 Protocol Deviations

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

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 trial performance and outcome 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 or inadequate trial performance (e.g., poor recruitment). (See Appendix A for the Data Safety Monitoring Plan.)

13.14.2 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, 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.

The CCC Safety/Medical Monitor is designated to independently review all safety events for this protocol, present it to the DSMB for periodic review, and provide PIs any Safety Letter when necessary. The Medical Monitor will determine which if any safety events require expedited reporting to NIDA, the DSMB and regulatory authorities. This will include events that are serious, related, and unexpected. Reports will be generated and presented for Data Safety Monitoring Board (DSMB) meetings.

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.

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

9.1.2.1. 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 the DSC.

14.3 Data Center Responsibilities

The DSC will 1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, 2) provide final guided source documents and eCRFs for the collection of all quantitative 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 data monitoring activities on study data collected from all study sites, and 6) perform data validation and cleaning activities prior to any interim analyses and prior to the final study database lock.

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 will be entered in Advantage eClinical in accordance with the instructions provided during protocol-specific training and guidelines established by the DSC.

The Principal Investigator at each site is responsible for maintaining accurate, complete and up-to-date research records. In addition, the investigator is responsible for ensuring the timely completion of 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. Data entry into the eCRFs shall be performed by authorized individuals only. Selected eCRFs may also require the investigator's electronic signature.

14.6 Data Editing

Data will be entered in Advantage eClinical. eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and forms are available to sites at all times in Advantage eClinical. These reports will be monitored regularly by the DSC. In addition, the DSC will identify inconsistencies within eCRFs and between eCRFs and post data clarification requests or queries in Advantage eClinical on a scheduled basis. Sites will resolve data inconsistencies and errors by entering all corrections and changes directly into Advantage eClinical.

14.7 Data Transfer/Lock

At the conclusion of data collection for the study, the DSC will perform final cleaning activities and will “lock” the study database from further modification. The final analysis datasets will be transferred to the Lead Investigator and to NIDA, as requested, for storage and archiving.

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

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

16.0 PROTOCOL SIGNATURE PAGE

SPONSOR'S REPRESENTATIVE (CCTN DESIGNEE)

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 3.0 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

Site Name _____

Node Affiliation _____

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grants from Mundipharma outside the submitted work. No further support from any organisation for the submitted work; no other financial relationships with any organisation that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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18.0 APPENDIX A: DATA AND SAFETY MONITORING PLAN

18.1 Brief Study Overview

Our central research question is: In settings with high need, limited resources, and differing staffing structures for managing opioid use disorder (OUD), what is the feasibility and impact of introducing a clinical protocol for OUD screening and buprenorphine (BUP, either as sublingual [SL-BUP] or extended-release [XR-BUP]) treatment initiation in the Emergency Department (ED) with referral for treatment?

Aims:

1. To evaluate using mixed methods the feasibility and acceptability of OUD screening, ED- initiated BUP, and referral.
2. Over the course of the study and as XR-BUP is added to hospital formularies, to estimate the percentage and confidence intervals of patients assessed, treated, and engaged in treatment at Day 30.

This will be a three-site study employing a multi-faceted approach to facilitate clinical protocol implementation and to assess feasibility, acceptability, and impact. We will develop, introduce and update site-specific ED clinical protocols and implementation plans for OUD screening, ED-initiated BUP, and referral for treatment. We will employ a participatory action research approach and use mixed methods incorporating data derived from:

1. Medical record and administrative data abstraction,
2. Research assessments involving patients who are eligible for and willing to receive ED-initiated BUP (including both those who do, and do not, receive BUP); these assessments will document the index ED visit and the 30th day after the index ED visit,
3. Qualitative interviews, focus groups, and quantitative assessments involving providers and staff, patients, and other stakeholders.

The intervention itself (BUP and referral) will be delivered as part of the facility's clinical protocol, rather than as a research procedure. The clinical protocol will be updated on an ongoing basis via a continuous quality improvement (CQI) process. Data abstracted from the electronic medical record (EMR) will be used to assess process measures including the primary clinical outcome of proportion receiving ED-initiated BUP amongst those who are eligible for and willing to receive this intervention. Secondarily, we will explore additional patient-level outcomes (engagement in ongoing treatment, drug use, overdose events, healthcare use, quality of life, etc.) by recruiting eligible and willing patients who received or did not receive ED-initiated BUP, to participate in two research visits. The baseline research visit, assessing clinical care received during the index ED 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, assessing engagement in treatment on the 30th day after the index ED 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. In addition, from each site, we will recruit ED and community providers and staff, ED patients, and other stakeholders to participate in qualitative interviews, focus groups, and quantitative assessments for the purpose of learning about patient-, provider-, and organizational-level barriers and facilitators to implementation and the resources needed to ensure that this intervention can be delivered in a way that is feasible, acceptable, and sustainable in these practice settings.

18.2 Oversight of Clinical Responsibilities

18.2.1 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, 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.

18.3 Data and Safety Monitoring Board (DSMB)

The NIDA CTN DSMB affiliated with this trial will be responsible for conducting periodic reviews of accumulating safety, trial performance, and outcome data. Reports will be generated and presented for Data and Safety Monitoring Board (DSMB) meetings. The DSMB will 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.

18.4 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 CCC and local Node monitors, as well as 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.

QA Site Visit Reports will be prepared by the NIDA CCC monitors following each site visit. These reports will be sent to the site Principal Investigator, site coordinator, the study Lead Investigator, Lead PM, and NIDA CCTN.

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.

18.5 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 separately from the study files and the medical records. No identifying information will be disclosed in reports, publications or presentations.

Participant Protection

This is a minimal risk observational and mixed-methods study. The decision to initiate BUP (or not) and the choice of formulation (SL-BUP or XR-BUP) will be a clinical decision made jointly by the participant and the provider. Participants will be evaluated for BUP administration as per local clinical guidelines.

18.6 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.

18.7 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 paper source documents and completion instructions. Data will be entered in 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 eCRFs may also require the investigator's electronic signature. In some situations, data collected on source documents will not be entered in Advantage eClinical, but when it is entered, it will follow the guidelines stated above.

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.

18.8 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.

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.

18.9 Database Lock and Transfer

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 analysis 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 parties for posting on Datashare, as well as storage and archiving.

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

19.0 APPENDIX B: METHOD OF INTRODUCING VARIABILITY BETWEEN SITES IN POWER SIMULATION

For either the before or after time period, we generate the implementation probability psite for each individual site using the following model:

$$\log\left(\frac{p_{site}}{1-p_{site}}\right) = \log\left(\frac{p_{alt}}{1-p_{alt}}\right) + \begin{cases} -\Delta, \text{ for site 1} \\ 0, \text{ for site 2} \\ \Delta, \text{ for site 3} \end{cases}$$

Where p_{alt} is shorthand for either p_{early} or p_{late}. So, p_{alt} is the implementation probability for site 2, and the mean of the logits of the implementation probabilities is always the logit of p_{alt}, but large values of Δ produce large differences between the site-level implementation probabilities p_{site}.

We explored the choices $\Delta = (0, 0.1, 1, 2, 3)$. Figure 6 shows how much Δ values affect the variability of the implementation probabilities across the sites. The results are based on the assumption that 180 patients will be identified and found eligible and willing to receive ED-initiated BP (available to assess the primary outcome).

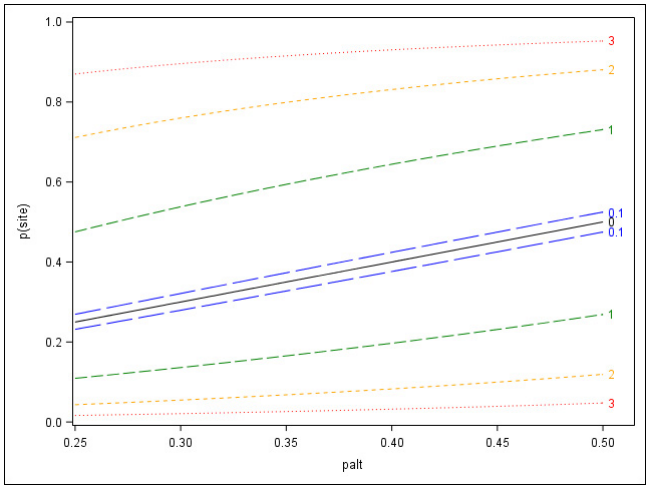

Figure 6: Site-level implementation probabilitiesp_{site} as a function of p_{alt} and Δ, for $0.25 \leq pp \leq 0.50$ and $\Delta = (0,0.1,1,2,3)$

The lines in Figure 6 are labeled with the Δ values used to generate them. The black solid line labeled 0 gives the implementation probability in site 2, which is always p_{alt} The lines below the 0-line give implementation probabilities for site 1, while the lines above the 0-line give implementation probabilities for site 3.

For example, when $\Delta = 2$ and $p_{alt} = 0.4$, the implementation probability for site 2 is 0.4 (black solid line), while the implementation probabilities for sites 1 and 3 are 0.08 and 0.83 (lower and upper orange dashed lines labeled “2”).