Project STAMINA

(Syringe service Telemedicine Access for Medication-assisted Intervention through Navigation)

Protocol Number: 1138-0420

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CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the Arnold Ventures Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection and Good Clinical Practice Training.

The protocol, informed consent documents, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 2/17/2022

Name*: Dennis P. Watson

Title*: Principal Investigator

Investigator Contact Information

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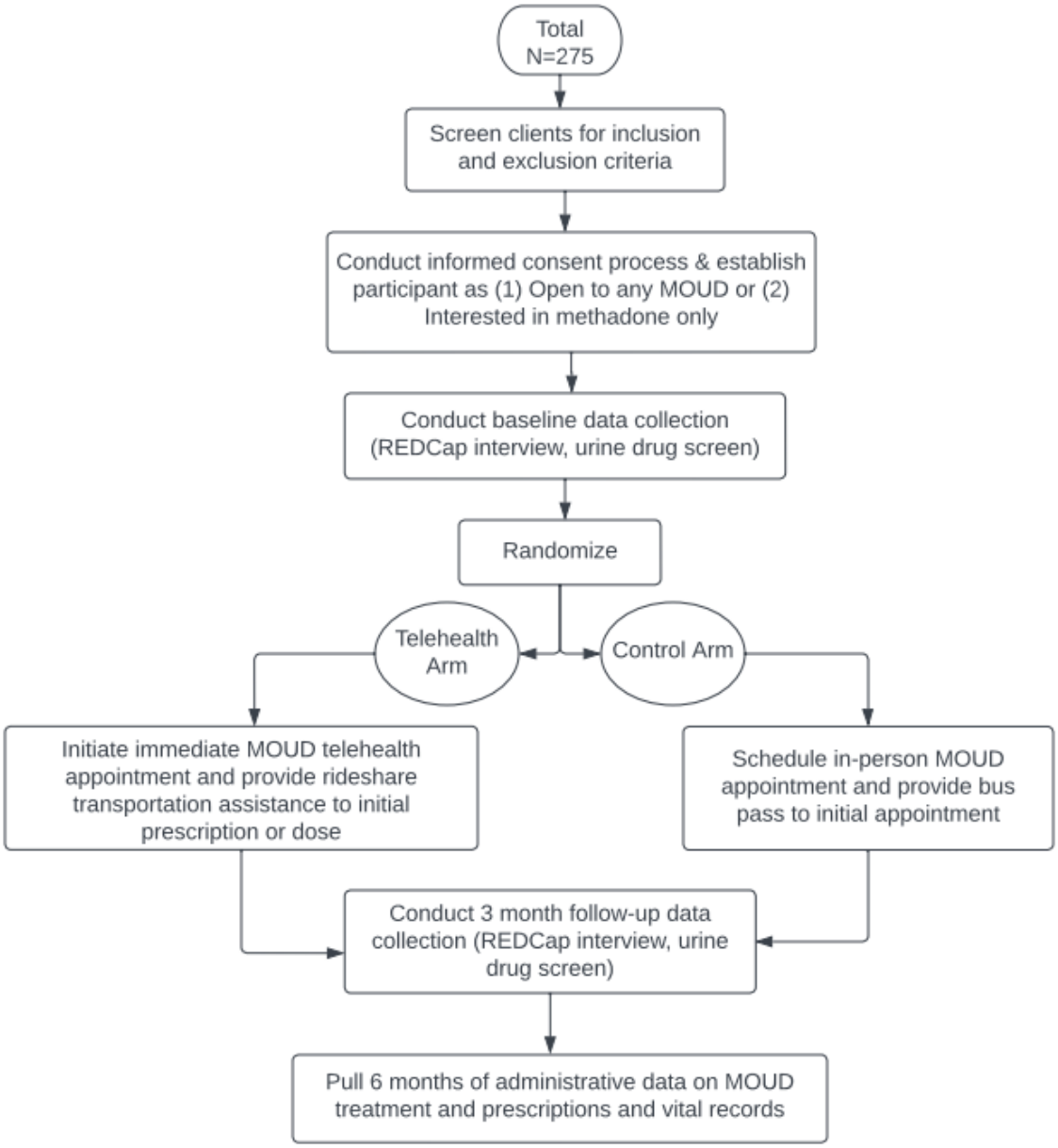
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Project STAMINA (Syringe Service Telemedicine Access for Medication-assisted Intervention Through NAvigation): Development and Testing of a Health Navigation Approach for Linking Syringe Service Program Clients to Medication Assisted Treatment
Grant Number:	Not applicable (the funder does not use grant numbers)
Study Description:	This clinical trial utilizes two study arms: (1) a treatment arm consisting of immediate telemedicine linkage and (2) a control arm consisting of standard referral to treatment. Half of the study participants are randomly enrolled in each arm. The study utilizes questionnaire data, drug test results, and administrative treatment data at multiple time points to determine what effect telemedicine linkage has on clients in relation to the comparison group. The primary hypothesis is that (1) STAMINA will be more effective at improving MOUD linkage than standard referral. Secondary hypotheses are: (2) the STAMINA participants will have greater MOUD engagement than participants who receive standard referral; (3) STAMINA participants will have greater MOUD retention than participants who receive standard referral; (4) STAMINA participants will have used less illicit opioids at follow-up than participants who received standard referral.
Objectives*:	The primary goal of this project is to establish effectiveness of a telemedicine approach for linking syringe exchange clients to medications for opioid use disorder.
Endpoints*:	Primary Outcome Measure: 1. Linkage to medication for opioid use disorder (MOUD) Secondary Outcome Measures: 2. Medication for opioid use disorder (MOUD) treatment engagement 3. Medication for opioid use disorder (MOUD) treatment retention 4. Self-report non-medication for opioid use disorder (MOUD) opioid use 5. Detected non-prescribed opioids

Study Population:	Inclusion criteria: (a) be able to communicate in English; (b) be at least 18 years of age; (c) reside in Cook County, Illinois; (d) demonstrate criteria for past year opioid use disorder as result of preliminary assessment; (e) express interest in receiving medication for an opioid use disorder (MOUD). Exclusion criteria: (a) have plans to move outside of Cook County, Illinois within the next 6 months; (b) have plans to serve a sentence that requires reporting to jail or prison within the next 6 months; (c) demonstrate severe opioid withdrawal symptoms at the time of enrollment as indicated by preliminary screening; (d) currently taking any form of medication that has been prescribed by a healthcare provider to treat opioid use disorder; (e) demonstrate inadequate ability to provide informed consent.
Phase* or Stage:	N/A
Description of Sites/Facilities Enrolling	University of Illinois Chicago Community Outreach Intervention Projects (COIP) Northwest and West Field Sites; Chicago, Illinois
Participants:	
Description of Study Intervention/Experimental Manipulation:	Participants in the telemedicine linkage intervention are immediately linked to telemedicine care with a physician waivered to prescribe medication for opioid use disorder (MOUD). The physician completes a virtual appointment, provides personalized care, and has the ability to prescribe MOUD that fits the patient's preferences and needs. Depending on the outcome of the telemedicine appointment, the participants is offered immediate transportation via ride share assistance to complete the initial steps related to their MOUD (i.e., pick up an initial buprenorphine prescription from a pharmacy, attend a methadone intake appointment, or receive an initial vivitrol injection).
Study Duration*:	28 months (August 24th, 2020-December 30th, 2022)
Participant Duration:	6 months

1.2 SCHEMA


Total N=275
Screen clients for inclusion and exclusion criteria
Conduct informed consent process & establish participant as (1) Open to any MOUD or (2) Interested in methadone only
Conduct baseline data collection (REDCap interview, urine drug screen)
Randomize
Telehealth Arm
Control Arm
Initiate immediate MOUD telehealth appointment and provide rideshare transportation assistance to initial prescription or dose
Schedule in-person MOUD appointment and provide bus pass to initial appointment
Conduct 3 month follow-up data collection (REDCap interview, urine drug screen)
Pull 6 months of administrative data on MOUD treatment and prescriptions and vital records

1.3 SCHEDULE OF ACTIVITIES

Table 1: Schedule of Activities

	Time point:		
Procedures:	**Enrollment**	**3 months post-enrollment**	**6 months post-enrollment**
Eligibility Assessment	*x*		
Informed Consent	*x*		
Contact & Locator Questionnaire	*x*		
Structured Questionnaire -Demographics -Social Support -Child Welfare -Housing -Alcohol Use -Opioid Cravings -Overdose Experiences - Drug Use & Treatment -Chronic Health Conditions -Psychological Health & Treatment -Trauma Exposure -Criminal Justice	*x*	*x*	
Urine Drug Screen	*x*	*x*	
Administrative/Secondary Data			*x**
**Data are pulled at a single time point and reflect the 6-month study duration for each participant.*			

2 INTRODUCTION

2.1 STUDY RATIONALE

Project STAMINA (Syringe Service Telemedicine Access for Medication-Assisted Intervention through Navigation) is a research study aiming to test the effectiveness of a linkage intervention that connects people with an OUD to MOUD using telehealth in a syringe service program (SSP) setting. STAMINA was conceptualized as a way to utilize a setting that is familiar to patients with an OUD to offer rapid access to care while removing barriers related to comfort.

The primary hypothesis is that (1) STAMINA will be more effective at improving MOUD linkage than standard referral. Secondary hypotheses are: (2) the STAMINA participants will have greater MOUD engagement than participants who receive standard referral; (3) STAMINA participants will have greater MOUD retention than participants who receive standard referral; (4) STAMINA participants will have used less illicit opioids at follow-up than participants who received standard referral.

2.2 BACKGROUND

U.S. opioid-related overdose deaths have more than quadrupled over the past 16 years, leading to an unprecedented rise in mortality rates [1, 2, 3]. Efforts to reverse these trends and reduce overdoses and associated fatalities have included expansion of medication for opioid use disorder. This includes Methadone, Suboxone®, and Vivitrol®, which have all been shown to improve recovery [4]. Despite efforts at expansion, people who use opioids experience considerable difficulties accessing MOUD because of long wait lists or lack of insurance that prevent immediate intake at a time when the patient is ready [5]. Syringe service programs (SSPs) are an excellent setting for linking those with an OUD to care, as they are judgement-free areas where people who use opioids feel more comfortable accessing services than they do in other healthcare settings [6]. SSPs have also already been demonstrated to lead to significant improvements in a number of other opioid-use related outcomes such as reduced transmission of communicable diseases (e.g., HIV), costs associated with treating them, and linkage to recovery-oriented services. Further, telemedicine will provide a way to immediately connect patients to a provider, thus eliminating the window between referral and appointment time where many patients are lost to treatment [6].

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The primary risks to participants of this study are (a) breaches of privacy (i.e., others would learn that participants are receiving treatment for an opioid use disorder) and (b) breaches of confidentiality (i.e., others would know the information obtained during data collection), which could result in stigma or criminal prosecution if it were discovered that the participant is an illegal opioid user. Additional risks to participants include (c) the possibility that they feel uncomfortable sharing information about themselves related to their current drug use or history with drug use and treatment, criminal justice involvement, or child welfare involvement or that (d) the questions may cause participants distress, particularly as these instruments include multiple items regarding sensitive issues.

2.3.2 KNOWN POTENTIAL BENEFITS

The possible benefits that participants might gain are (a) the opportunity to discuss and reflect on their recent experiences and (b) the opportunity to inform research that may lead to the future development of improved linkage to treatment for individuals with opioid use disorder.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The collection of sensitive data (e.g., data pertaining to illicit drug use) and identifiable data is necessary to assess the proposed outcomes and examine the effect of the telemedicine linkage intervention. Study procedures aim to minimize risks associated with the collection of these data through the following ways: (a) all data collected during participant interactions (i.e., structured interviews and drug screens) will be entered directly into Research Electronic Data Capture (REDCap) to ensure secure data storage that is HIPPA compliant and that that only relevant research team members have access to this

information; (b) all administrative MOUD treatment data and vital records data collected on participants will be stored in a HIPPA compliant Box Health folder that only relevant research team members can access or entered and stored in REDCap or; (c) all paper forms used in the consent process will be temporarily stored in a locked cabinet at the enrollment sites and then transferred by the study's Project Manager for long-term (i.e., three years) storage in a locked cabinet within the Principal Investigator's office; (d) research staff will assure all participants throughout the structured interviews that they may choose to skip any questions they do not want to answer and will end the interview or skip a question if a participant seems distressed about sharing the information requested.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Assess the intervention's effectiveness at linking clients to MOUD treatment.	Linkage to MOUD treatment	The primary goal of the intervention as it is designed is to link clients to MOUD treatment.
Secondary		
Assess the intervention's effectiveness at improving MOUD treatment-related outcomes.	MOUD treatment engagement	These outcomes should improve following linkage to MOUD treatment.
	MOUD treatment retention	
Assess the intervention's effectiveness at decreasing illicit opioid use.	Self-report non-medication for opioid use disorder (MOUD) opioid use	These outcomes should improve following MOUD treatment engagement and retention.
	Detected non-prescribed opioids	

4 STUDY DESIGN

4.1 OVERALL DESIGN

Our primary long-term goal is to establish an effective telemedicine method for linking individuals with OUD to MOUD from the SSP. The primary hypothesis is that (1) STAMINA will be more effective at

improving MOUD linkage than standard referral. We expect the program will have a positive effect on client recovery outcomes, and we will be able to identify specific program elements or processes that drive these outcomes.

For the study, syringe exchange clients at any of two SSP sites operated by the University of Illinois Chicago who express interest in participating in the research study are first screened for eligibility by an onsite research assistant. If eligibility criteria are met, the research assistant completes the informed consent process and obtains a signature of consent. Participants are subsequently assigned to one of two study arms using randomization with stratification by study site and whether or not they indicate a strong preference for methadone treatment, which is determined during the eligibility screening. Study arms include: (1) the intervention arm, in which participants are immediately linked to telemedicine care with a physician waivered to prescribe medication for opioid use disorder treatment and (2) the control arm, in which participants receive a standard referral to an in-person appointment-as would normally happen in the SSP sites.

To randomize participants, an offsite research assistant is immediately alerted of the new enrollment and informed of their medication preference, checks the pre-established randomization lists, and requests a telemedicine appointment when applicable. Meanwhile, the onsite research assistant responsible for enrolling the participant conducts all baseline data collection, including a structured interview and urine drug screen. At the completion of baseline data collection, the onsite research assistant and participant are informed of the study arm assignment and move forward with completing or scheduling the appropriate appointment type.

For participants of the intervention arm, the research assistant prepares the participant for their telemedicine appointment, assists in completion of the appointment, and offers a ride share for the participant to pick up their prescription or initiate dosing. For participants of the control arm, the research assistant schedules an in-person appointment and offers bus passes for their first appointment.

Participants are asked to return to the study site to complete follow-up data collection, including another structured interview and urine drug screen, at 3 months.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The control condition was defined in consultation with our SSP partner based on usual services they provide to clients they serve. Therefore, the control reflects real-world service options that would be available to participants outside of the study's conditions.

Despite the benefits of utilizing a control arm that is representative of the typical care, it is difficult to identify to where SSP staff refer clients, as it is not ethical to require them to send patients to providers the research team has relationships with if they are not the best fit for the patient's needs. Additionally, with the onset of the pandemic, and loosening of treatment regulations, many patients have telemedicine MOUD linkage options available to them that are similar to the treatment condition (the study was conceived of and funded prior to the start of the COVID-19 pandemic, but data collection did not start until after).

4.3 JUSTIFICATION FOR INTERVENTION

The telemedicine linkage intervention being tested in this study aims to provide a solution to access-related barriers experienced by patients with opioid use disorder who are seeking treatment. The rational for implementing telemedicine linkage within a syringe service program (SSP) is because these sites are considered trusted settings in which high-risk opioid users feel comfortable obtaining care while also offering the potential for rapid connection to care following an interest in treatment. It is important to note, the intervention was developed in collaboration with medical and SSP partners as a potential solution to access barriers existing prior to the loosening of telemedicine treatment regulations that occurred with the onset of the COVID-19 pandemic.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if they have completed the baseline assessment and the 3-month follow-up assessment.

The end of the study is defined as the end of the 6-month period for which we have permission to access the participant's administrative health data, as shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Inclusion criteria for the study includes:

1. communicate in English
2. be at least 18 years of age
3. reside in Cook County, Illinois
4. demonstrate clinical criteria for a past year opioid use disorder
5. express interest in receiving medication for an opioid use disorder (MOUD)

5.2 EXCLUSION CRITERIA

Exclusion criteria for the study includes:

1. have plans to move outside of Cook County, Illinois within the next 6 months
2. have plans to serve a sentence that requires reporting to jail or prison within the next 6 months
3. be experiencing severe opioid withdrawal symptoms (that would indicate the need for more immediate intervention) at the time of enrollment
4. currently taking any form of medication that has been prescribed by a healthcare provider to treat opioid use disorder
5. demonstrate inadequate ability to provide informed consent, as indicated by poor understanding of research protocols explained to them

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not entered into the study because they do not meet the inclusion or exclusion criteria (i.e., failure of screening). If research staff learn that the information provided by someone previously consented to the study was inaccurate (for example, if a research staff member learns from a participant during their baseline or follow-up assessment that they do not use opioids or are already receiving a medication for opioid use disorder) then data collection will be discontinued, and the participant will be excluded from the study. The patient will still be provided with the related study compensation for their time.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Strategies for Recruitment

Potential participants will be recruited one of the following ways: (1) individuals will see the STAMINA poster within the SSP service site and be able to ask SSP staff where to get more information, (2) current syringe service clients will be able to inform staff that they are interested in treatment for an opioid use disorder, and staff will inform them of the study opportunity, (3) individuals will see a STAMINA flyer at another social service program in the city or on social media platforms and be able to call study personnel for more information on the study, or (4) individuals will be introduced to the study by Chestnut Health street outreach staff. Details on each method of recruitment are provided below.

(1 or 2) For individuals already on site, any interested SSP client will be informed by SSP staff that a study possibility exists for individuals interested in medication for opioid use disorder and if they would like to learn more information about the study, the staff can introduce the client to the research personnel. They will utilize the SSP recruitment script to explain the study. With their verbal permission, they will be introduced to the research staff who can complete the full recruitment script, eligibility assessment, and enrollment process with a research assistant.

(3) For individuals offsite that see a flyer from another social service provider or through a social media platform, they will first briefly speak with a research assistant by telephone to complete initial screening and then be scheduled for an in-person time at SSP to complete the full recruitment script, eligibility assessment, and enrollment process with a research assistant.

(4) Chestnut Health Systems' Lighthouse Institute staff will utilize their street outreach procedures, during which they enter communities and engage community members to inform people of the study opportunity. For STAMINA, the street outreach workers will stay within Chicago's Austin and Humboldt Park neighborhoods since that is where our two SSP study sites are located. The street outreach will (a) approach people in public areas, such as street corners, bus stops, and parks. They will then (b) implement the study recruitment script, which is written broadly enough that it does not assume the person they are approaching is an opioid user and therefore, allows them to openly introduce the study

opportunity without needing to specifically look for any signs of opioid use prior to approaching individuals. For anyone who does indicate that they are interested, the street outreach worker will then (c) assess for initial eligibility and (d) offer immediate transportation back to the SSP site. Once they arrive at SSP, they will meet with a study research assistant to complete the full recruitment script, eligibility assessment, and enrollment process.

If an individual is at an SSP and is interested in participating in the study but does not have the available time that day or does not feel ready to begin treatment that day, we will offer for them to sign a "Consent to Contact" form. The form will give us permission to contact them within the next few days-weeks to see if they are interested in participating. If so, we will be able to schedule a time for them to come in and complete the enrollment process. This will ensure that there is availability, and that the client has time in their schedule. This form will be offered but not required; they will only sign if interested.

Strategies for Retention

Regarding participant retention related to the follow-up data collection, research staff will make every effort to contact participants and schedule them for their 3-month survey and urine drug screen. This includes the collection of multiple forms of contact information (details can be found under Section 8.1 Endpoint and Non-Safety Assessments), as well as continuous attempts throughout the allowable follow-up window (i.e., 1 month prior the 3-month due date - 2 months following the 3-month due date).

Participant retention related to the intervention is not applicable, as it is left to the discretion of the participant whether they complete steps related to their MOUD care.

Participant Incentive

Participants will be compensated for both baseline data and follow-up data collection at the conclusion of each visit. At baseline, participants will receive $50 for completing all study activities. At the 3-month time point, participants will receive $25 for completing the questionnaire and an additional $10 for completing the urine drug screen. All payments will be given to participants in the form of a VISA gift card. Should the participant be unable to visit on-site and complete data collection only by phone, their gift card will be mailed to them at an address they provide.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

This study includes both an intervention and control condition.

Intervention Arm (1): Participants enrolled into the telemedicine linkage intervention will be immediately linked to telemedicine care with a physician waivered to prescribe MOUD treatment. All enrollment and telemedicine care will occur at the University of Illinois Chicago (UIC)'s School of Public Health's Community Outreach Intervention Project (COIP) SSP sites. On-site, the participant will have their vitals checked (i.e., temperature, blood pressure) by a research team member and be connected with a University of Illinois (UI) Health Mile Square Health Center physician (Chicago, Illinois) via telemedicine linkage on a tablet computer. The research assistant will share the participant's vitals with the physician, and the physician will complete a virtual appointment and assessment during which they will provide personalized care. Related to the appointment, the physician will make notes in the patient's electronic medical records of their treatment plan. The physician will have the ability to prescribe buprenorphine. Should the participant receive an induction prescription for buprenorphine or naltrexone, it will be sent to the Mile Square Health Center (MSHC) pharmacy or a pharmacy of the participant's choice. If the participant does not have medical insurance, the MSHC pharmacy will be able to assist with prescription costs. Additionally, the participant will be provided with instructions for how to locate the pharmacy on-site at the FQHC and how to complete induction steps.

Depending on the MOUD preference and whether any medications are prescribed on the telemedicine visit, the research assistant will offer the participant transportation via ride share to complete their initial steps in the process of beginning MOUD. If the participant is prescribed buprenorphine on the telemedicine visit, they will be provided with a rideshare to the pharmacy to pick up the prescription. If the participant is referred to methadone, they will be provided with a ride share for their first in-person appointment for the methadone intake. If the participant is scheduled for a vivitrol injection, they will be provided with a rideshare to the pharmacy to pick-up any medication prescribed for injection preparation or to their initial injection.

All follow-up OUD care and prescribing will be conducted based on the provider's standards and may include in-person or telemedicine appointments. Should the provider deem an in-person intake appointment clinically necessary for any participant assigned to the treatment arm, the research assistant will provide a full-day bus pass to assist with transportation.

Standard Care Arm (2): Participants enrolled in the control arm will receive a standard referral to an in-person appointment with an MOUD provider, which will typically occur within 24-72 hours of the enrollment time, depending on provider and participant availability. Regarding scheduling, this will include UI Health MSHC healthcare providers for participants interested in discussing their MOUD options, or who are open to receiving buprenorphine or vivitrol. For participants who are strictly interested in methadone, this will include UI Health MSHC's Family Guidance methadone providers, additional Family Guidance methadone providers across Chicago, or another methadone provider with a location convenient to the participant. The research assistant will provide two bus passes to cover the transportation to and from the appointment.

All follow-up OUD care and prescribing will be conducted based on the provider's standards and may include in-person or telemedicine appointments.

6.1.2 ADMINISTRATION AND/OR DOSING

Not applicable.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Fidelity assessments with the research assistants will ensure compliance with the study procedures and adherence to the intervention design. A checklist of critical components and their associated tasks will guide the fidelity audits. The project manager will conduct virtual or in-person fidelity assessments with research assistants monthly. Any concerns or issues will be reviewed with the research assistant and corrected.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants will be assigned to one of the two study arms (i.e., telemedicine or standard in-person referrals) using randomization with stratification by site and whether they indicate a strong preference for methadone treatment. The reason for stratifying assignment on this second condition is to avoid potential confounding of the results since methadone treatment might be administered by a different provider and would require different linkage procedures after the telemedicine call. Arm allocation will be determined in advance of enrollment by randomizing pre-established study identification numbers that will be sequentially assigned to participants as they are enrolled.

To minimize bias during data collection, two research assistants (one offsite and one onsite) will share the enrollment responsibilities. During enrollment, the onsite research assistant will screen the client for eligibility, which includes an assessment of the client's interest in MOUD and determination of their preferred medication. Due to the need for scheduling a telemedicine appointment at least 1 hour in advance, an offsite research assistant will then be notified that a client is consented to the study, of their enrollment site, and of their specific medication preference. The onsite research assistant and participant will move forward with baseline data collection remaining blinded to the study arm assignment while the offsite research assistant checks the pre-established randomization list and schedules a telemedicine appointment when necessary. The offsite research assistant will inform the onsite research assistant of the arm assignment once baseline data collection is complete.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Not applicable; The intervention focus is linkage and does not require participants to adhere to any protocols.

6.5 CONCOMITANT THERAPY

Not applicable.

6.5.1 RESCUE THERAPY

Not applicable.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

This linkage intervention aims to connect participants to MOUD treatment, but the completion of the telehealth appointment, in-person MOUD appointment(s), or accessing prescriptions is at the discretion of the participant. Participants may choose not to take part in the initial linkage appointment (i.e., telehealth or in-person) or to adhere to any subsequent treatment-related activities (e.g., prescription pick-up, follow-up appointments) and still remain a participant of this study.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. If a participant wishes to discontinue their involvement with the study or forgo follow-up data collection activities, they are able to notify any study team member or the IRB at any time to withdraw.

Investigators may discontinue a participant from the study for the following reasons:

- The participant (a) does not meet an inclusion criterion or (b) meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

Withdrawal from the study will not adversely affect the participant. Participants are free to continue to receive their MOUD treatment or SSP services even if withdrawn. Should a participant withdraw, we will not request further data collection activities and will remove any existing data from the sample.

The reason for participant discontinuation or withdrawal from the study will be recorded. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, are randomized, and receive the study intervention, and subsequently withdraw, or are discontinued from the study will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for their 3-month study visit within 5 months of their enrollment date (i.e., 2 months following their 3-month follow-up date).

The following actions will be taken to improve the likelihood that participants will complete their 3-month study visit within the permitted window.

- Research staff will collect at least 3 sources of contact information at enrollment and will verify its accuracy before the participant leaves the enrollment site.

- Research staff will complete contact verification checks leading up to the 3-month study visit and begin attempting to schedule the follow-up visit 1 month prior to the 3-month post-enrollment date.
- Research staff will provide reminder calls/texts/emails/mail, reschedule missed visits, and discuss the importance of follow-up data collection with the participants.
- If necessary, research staff will complete follow-up data collection by telephone and forgo the urine drug screen data collection if the participant refuses travel, proves to be difficult to contact, or no-shows scheduled appointment(s).
- Before a participant is deemed lost to follow-up, research staff will make every effort to regain contact with the participant.
- All contact attempts will be documented in the participant's study file.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

The study will utilize the following procedures, measures, and assessments during eligibility screening and data collection.

Following recruitment, research staff will be responsible for completing an assessment of eligibility for each potential participant. In doing so, they will assess language spoken, age, county of residence, plans for relocation, and plans for serving criminal sentence(s). If the client reports that they have plans to move outside of Cook County or to serve a prison or jail sentence within the next 6 months, they will be excluded. Research staff will clarify with the client that, for the purpose of this study, place of residence refers to where the client most often sleeps. If clients have unstable housing or have a permanent mailing address that is different from where they regularly sleep, we will refer to where they sleep most days as their county of residence.

Next, the research assistant will administer the DSM-5 for Opioid Use Disorder [7]. The client must answer "yes" to at least 2 items on the scale, indicating signs of a mild opioid use disorder within the past 12 months. The research assistant will also administer the Clinical Opioid Withdrawal Scale (COWS) [8], for which we have developed protocols with input from an addiction medicine specialist to ensure it can be administered easily by non-clinician research assistants. Clients who score 36 or more on the scale will be excluded, as this is an indication of severe withdrawal. [Note: These clients will be provided an immediate referral to care with a physician despite being excluded from the study.]

The research assistant will then discuss the Opioid Use Disorder Treatment Comparison Overview, which is a shared decision-making tool created by the research team that provides a visual explanation of all 3 MOUDs (i.e., buprenorphine, naltrexone, and methadone). During this discussion, the research assistant and client will walk through the treatment options and confirm the client's MOUD treatment interest. As long as the client expresses interest in at least 1 of the 3 medication types then they meet eligibility requirements. It is also at this point that the research assistant will clarify which type of MOUD the client is initially interested in (though they will be allowed to change their minds). The research assistant will clarify whether the client is initially interested in suboxone or vivitrol, or initially open to considering

these MOUDs, OR only initially interested in methadone. [This clarification will be used in the blocking randomization described previously under "6.3 Measures to minimize bias: Randomization and blinding".]

Finally, the research assistant (i) asks the client to take a urine drug screen. If they are negative for buprenorphine or methadone, the research assistant will move forward. If they are positive for either medication, the research assistant will ask the client if they are currently taking "x" medication as a part of a prescribed treatment plan. If they are taking medication they purchased through the illicit drug market, then the research assistant will move forward. If they are already taking medication that is prescribed, they will be excluded.

Research assistants will continue to read the full recruitment script with eligible clients and complete the informed consent process for anyone meeting all criteria and interested in participating. The research assistant will begin data collection with all consented participants. This includes a 45–60-minute structured interview that is collected in the Research Electronic Data Capture (REDCap) data collection system. This interview covers the following topics:

1. Full name, Date of Birth, SSN (used for locating purposes), and UI Health Medical Record Number (MRN)
2. Demographic information
3. Social support
4. Child welfare involvement
5. Housing and homelessness
6. Alcohol use
7. Drug use
8. Heroin cravings
9. Opioid withdrawal symptoms
10. Overdose experiences
11. Physical and mental health
12. Trauma exposure
13. Criminal justice involvement
14. Treatment motivation
15. Quality of life

The interview will also request participant contact information (i.e., Client Contact & Locator Form). This information will not be used as research data, but rather, will aid the scheduling of research follow-up visits. The form will ask participants for (1) their contact information, (2) the contact information for others who might be able to help in reaching the participant, (3) the contact information for providers whose services they utilize and might be able to help reach the participant. Additionally, all participants will have submitted a urine drug screen during recruitment, and this will also be used as a form of data. The results of the screen will be entered into REDCap with the participant's interview data. All participants will be asked to complete the REDCap interview and a second urine drug screen at 3-months. Participants will be asked to return to the recruitment site to complete these activities; however, participants can be accommodated to complete the interview by phone and forgo the drug screen when necessary.

Lastly, as part of data collection, we will access the participant's protected health information (PHI) from the four sources listed below.

- (1) Mile Square Health Center and (2) Family Guidance Center Records: We will request MOUD treatment data from Mile Square Health Center and Family Guidance Center. These data will be used to understand participant MOUD linkage, engagement, and retention. These data will include dates of service, medications prescribed, and treatment details to understand compliance. The same data will be pulled for participants in both arms. Note: We recognize that not all patients will go to Mile Square Health Center or Family Guidance Center after their appointment or referral, but we plan to access these medical records for any consented participant. Participants will not be withdrawn from the study should they not be treated at MSHC or Family Guidance, as this is an intent to treat study. Thus, we will have to rely on self-report data for participants who choose to be treated elsewhere.

- (3) Illinois Prescription Monitoring Program (PMP) Records: We will request dispensation data for buprenorphine from the Illinois Prescription Monitoring Program. Though we ask participants to self-report whether they have engaged in medication for opioid use disorder treatment, the PMP data will allow us to verify whether they have been dispensed any of the prescriptions. This helps us to understand the nature of whether a participant is involved in treatment.

- (4) Illinois Vital Records: We will collect Vitals Record data for the purpose of verifying whether a participant passed away. We understand that individuals who use drugs are at the risk of overdose, or other drug-related health issues which can lead to death, and while our goal is to enroll these clients in treatment, the possibility of relapse or health issues remain present. Thus, we are obtaining this data to verify if a participant disengaged from the study because of death and to understand whether that death was caused by drug use.

8.2 SAFETY ASSESSMENTS

Not applicable.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention related***.

This will include the following: mental health-related outpatient treatment; criminal arrests, bookings, or charges; criminal detainment or imprisonment; new chronic health condition.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An adverse event (AE) or suspected adverse reaction is considered "serious" if it results in any of the

following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

This will include the following: death; attempted suicide; overdose-related ER visit; overdose-related hospitalization; mental health-related hospitalization.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study procedures, there is a reasonable possibility that the study procedures caused the AE, or there is a temporal relationship between the study procedures and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.
- **Not Related** – There is not a reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures and event onset, or an alternate etiology has been established.

OR

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

Unanticipated AEs are events that are not consistent with the foreseeable risk associated with research procedures or are not expected in the natural progression of any underlying condition of the sample. The AEs and SAEs identified in Sections 8.3.1 and 8.3.2 are anticipated as they are commonly associated with the course of OUD. Per Chestnut Health IRB policies, all deaths are considered unanticipated events.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel when (a) attempting to contact the participant to schedule their 3-month follow-up or (b) during the 3-month study follow-up.

(a) If study staff are notified of a participant death while attempting to make contact for their follow-up data collection, they will complete an "Adverse Event Form" for submission to the IRB. Per the Chestnut Health IRB policies, all studies are to report unanticipated events to the IRB's Human Protections Administrator within 2 business days of PI notification.

(b) Study staff will learn of other AEs or SAEs during the 3-month study follow-up. For anticipated events, information will be reported at study-end reporting on Clinical Trials.gov. For unanticipated events, information will be reported to the IRB's Human Protections Administrator within 2 business days. With the assistance of a clinician with expertise in opioid use disorder, it will be determined whether the adverse event is related or unrelated to the study procedures or intervention.

Additionally, subject withdrawals and complaints will be monitored by the PIs with assistance from the Project Manager to ensure study procedures designed to protect the privacy and confidentiality of participants are adequate and no unanticipated distress or unintended outcomes have resulted from any of the study procedures.

8.3.5 ADVERSE EVENT REPORTING

Unanticipated adverse events will be reported to the IRB within 2 business days. Adverse events related to the study will be reported in annual reporting to the IRB. All adverse events, whether related or unrelated and anticipated or unanticipated, will be reported at the study conclusion on Clinical Trials.gov.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Unanticipated serious adverse events will be reported to the IRB within 2 business days. All deaths will be considered unexpected. Serious adverse events related to the study will be reported in annual reporting to the IRB. All adverse events, whether related or unrelated and anticipated or unanticipated, will be reported at the study conclusion on Clinical Trials.gov.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.9 REPORTING OF PREGNANCY

Not applicable.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

Not applicable.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

Not applicable.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary:
  - Null: No difference in treatment linkage rates will be observed between the treatment and control arms.
  - Alternative: There will be a difference in treatment linkage rates between the treatment and control arms.
- Secondary 1:
  - Null: There will be no difference in MOUD treatment engagement between the treatment and control arms.
  - Alternative: There will be a difference in MOUD treatment engagement between the treatment and control arms.
- Secondary 2:
  - Null: No difference in MOUD treatment retention will be observed between the treatment and control arms.
  - Alternative: There will be a difference in treatment linkage rates between the treatment and control arms.
- Secondary 3:
  - Null: No difference in illicit opioid use will be observed between the treatment and control arms.
  - Alternative: A difference in illicit opioid use between treatment and control arms will be observed.

9.2 SAMPLE SIZE DETERMINATION

A power analysis determined a minimum sample size of n = 273 is needed to detect an odds ratio of 2.0 for a binary predictor (the intervention effect) in a logistic regression with 80% power. The control group's proportion of successful treatment initiation was set at 0.35. Assuming an 80% study retention rate across all three waves of data collection, the recruitment goal has been set at n = 350 total participants (n = 175 for each arm).

Due to circumstances encountered during the study period (i.e., disruptions due to COVID-19 pandemic), study recruitment did not reach the target sample size. The final sample included 274 baseline participants and 221 follow-up interviews (80% retention). With a sample size of N=221, the minimum detectable odds ratio at alpha=.05 and 80% power is 2.16.

9.3 POPULATIONS FOR ANALYSES

Primary outcome analyses of treatment engagement will be conducted on the sample of all randomized participants, i.e., intention-to-treat (ITT) sample. Analyses of treatment retention will include all participants who initiated treatment within 14 days of the baseline visit. Sensitivity analyses will test alternative treatment initiation cutoffs.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

We will compute descriptive statistics on quantitative measures, reporting frequencies and percentages for categorical variables, and means and standard deviations, or medians and interquartile ranges for continuous variables. All inferential tests will be 2-tailed; we will report 95% confidence intervals and exact p-values. Pre-specified covariates are listed in the sections below.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Primary Outcome: Linkage to medication for opioid use disorder (MOUD)

We will use multivariable, binary logistic regression models with linkage to MOUD (yes/no) as the dependent variable. Linkage will be defined as visiting the treatment provider within 14 days post-enrollment, based on electronic medical records (EMR). In the event that EMR data is not available for some participants (i.e., participants who received care at a clinic without a study affiliation), we will substitute self-report data for those records and conduct a sensitivity analysis. Participants lost to follow-up will be coded as not linked to treatment.

The primary independent variable in these models will be a dichotomous indicator for treatment condition (0 = CC; 1 = TC). Control variables will include at a minimum: demographics (age, sex, race/ethnicity), baseline severity of substance use disorder, baseline severity of psychological distress, and past overdose experiences. We will also control for treatment preference (methadone only vs. any MOUD), and location (a dichotomous variable representing each of the COIP sites.) If covariate missingness is greater than 10% we will use multiple imputation; otherwise, we will use complete case analysis. Results will be presented as odds ratios with 95% confidence intervals, and predicted probabilities. Alternatively, the outcome can be modeled using robust Poisson regression to obtain risk ratios with 95% confidence intervals.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary Outcome Measures:

- *Medication for opioid use disorder (MOUD) treatment engagement*
- *Medication for opioid use disorder (MOUD) treatment retention*
- *Self-report non-medication for opioid use disorder (MOUD) opioid use*
- *Detected non-prescribed opioids*

The analytic sample for secondary outcomes will include participants linked to treatment after the baseline visit. We will use multivariable, binary logistic regression models with engagement (yes/no) and retention (yes/no) as dependent variables. Engagement will be defined as making at least 2 visits to the treatment provider within 34 days post-enrollment. Retention will be defined as going no more than 14 days without medication for opioid use disorder or being discharged from care within 3 months post-enrollment.

The primary independent variable in these models will be a dichotomous indicator for treatment condition (0 = CC; 1 = TC). Control variables will include at a minimum: demographics (age, sex, race/ethnicity), baseline severity of substance use disorder, baseline severity of psychological distress, and past overdose experiences. We will also control for treatment preference (methadone only vs. any MOUD), and location (a dichotomous variable representing each of the COIP sites.) If covariate missingness is greater than 10% we will use multiple imputation; otherwise, we will use complete case analysis. Results will be presented as odds ratios with 95% confidence intervals, and predicted probabilities. Alternatively, the outcome can be modeled using robust Poisson regression to obtain risk ratios with 95% confidence intervals.

Illicit drug use at follow-up will be measured as a dichotomous variable (presence/absence in urine), and modeled in a similar fashion using multivariable, binary logistic regression models.

Treatment engagement at follow-up can also be modeled as a count variable (number of sessions attended per unit time) using Poisson or negative binomial regression; or treated as continuous if normality assumptions are met and modeled using ordinary least squares regression.

An alternate measure of engagement is to assess how long each participant remained in treatment defined as being either the last treatment appointment kept, or participant's self-report of the date they discontinued using buprenorphine. The time to discontinuation of treatment/medication can then be modeled using survival analysis or proportional hazard models. These models provide information on how long persons remain in treatment allowing comparisons of the survival times (or conversely, periods of highest risk for dropping out of treatment) by study condition. If the proportional hazards assumption is met, we will use Cox regression; otherwise, we will use an accelerated failure time model such as Weibull regression.

9.4.4 SAFETY ANALYSES

Not applicable.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

We will compare the intervention groups on demographics (age, sex/gender, race/ethnicity, education), socioeconomic indicators (employment, housing, insurance), baseline substance use (self-report and urine test), overdose, substance use treatment history, chronic health conditions, criminal-legal system involvement (arrest, jail/prison, probation/parole), and psychosocial measures (trauma symptoms, depression, serious mental illness). We will compute chi-square tests and report exact p-values.

9.4.6 PLANNED INTERIM ANALYSES

Not applicable.

9.4.7 SUB-GROUP ANALYSES

We will conduct sub-group analyses on primary and secondary endpoints by treatment preference (methadone only vs any MOUD), and by race/ethnicity (Black/African American vs. other). Sub-groups for other characteristics (e.g. sex/gender) are not likely to have sufficient numbers.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed.

9.4.9 EXPLORATORY ANALYSES

Not applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant, and written documentation of informed consent will be completed prior to starting the study intervention. The following consent materials are used during this process: (1) consent form, (2) list of competency questions, (3) health information release form, (4) locator release form.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Once the initial eligibility has been determined during the screening process, the research assistant will provide the client with a copy of the consent form and keep one for themselves. Consent documents will be provided in English only, as English-speaking abilities are required for eligibility. Together, they will discuss the consent form in detail. Once the consent document has been fully reviewed, the research

assistant will check for the final eligibility criteria by asking three questions to the client to verify that the client is able to participate per their level of competency. The questions include:

a) Can you repeat to me the purpose of the study? (*Participant must indicate they know we are interested in treatment linkage or studying linkage to medication.*)
b) Do you remember how long this process (i.e., enrollment and intervention) could take today? (*Participant must indicate 2-3 hours*.)
c) Do you remember what you should do if you decided you no longer wish to take part in the study after leaving here? (*Participants must indicate that they know to contact the research team or IRB and let them know*.)

If the client is able to answer these questions, they will be deemed eligible. The research assistant will ask the client to print, sign, and date the form; the research assistant will do the same.

In addition to the consent form, the research assistant will also review two additional forms: a (1) health information release for the methadone provider, which permits the study team to access methadone treatment data from the external methadone provider (i.e., Family Guidance) for the participant's study 6-month window, and (2) locator release form for participant tracking purposes, which permits the study team to speak with the contacts provided by the participant about the participant's whereabouts and latest contact information. The research assistant will go through the forms' contents in full detail and allow the participant to ask questions. The participant will be asked to sign each form at the conclusion of the review.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency, and/or regulatory authorities. If the study is prematurely terminated or suspended, the principal investigators will promptly inform the Institutional Review Board (IRB) and sponsor/funding agency and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, or other relevant regulatory or oversight bodies (DSMB).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable

information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

We will collect the questionnaire data in REDCap and keep it stored there through the duration of the study. REDCap is password protected and HIPAA compliant; user access to this database will be restricted to those who collect, manage, or clean this data. Additionally, we will store the urine drug screen drug screen in this same REDCap database for the duration of the study. The participant IDs will be connected to the participant's name within REDCap.

Secondary data will be obtained from each source utilizing secure procedures. We will provide the designated data manager with an Excel spreadsheet containing Name, DOB, gender, race, and last 4 of SSN of individuals we are requesting data for. We will upload this file to a UIC Box Health folder, which will be separate for each organization and created specifically for data sharing related to the study that we will give the data manager access to. We will inform them when the file is uploaded and ask them to inform us when they have downloaded it. After they have downloaded the file, we will delete it from the Box Health folder. After pulling these data, the data manager will send it back to us, using a secure ID as the only identifier. They will inform us when they have uploaded the data to the Box Health folder and we will then move the data to another Box Health study folder that only appropriately designated study personnel will have permissions to access. They will send the master list of secure ID linked with the identifiers in a separate file, which will be stored in the same manner. Identifiers will be removed once the data are linked. Data will be stored using the participant study ID, only.

For Chestnut Health Systems analysts involved in the various outcomes analyses, the data will be shared via a Chestnut Box Health folder. This will exclude contact or identifying information. We will upload the dataset to the folder, provide them with access, and then they will be able to download the file to conduct the analyses. All analysts will follow measures to ensure the confidentiality of the data, as outlined in their contracts. At the end of the study, all study databases will be de-identified and archived by a study team member.

Further, all research activities, including baseline and follow-up data collection, will be conducted in as private a setting as possible so that answers shared with the research assistant cannot be overheard by others.

Additionally, we have received a Certificate of Confidentiality (COC) from NIH to provide an additional layer of protection for participants. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceedings, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Interview and secondary data collected for this study will be analyzed and stored by UIC and Chestnut Health Systems researchers. After the study is completed, the de-identified, archived data will be stored

with Chestnut Health Systems for use by other researchers including those outside of the study following the rules and procedures established in Chestnut Health System's data sharing policies.

Specimens collected for the urine screens will not be stored long-term; results of the screens will be entered into REDCap, and specimens will be immediately discarded.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Principal Investigator**
Dennis Watson, PhD	*James Swartz, PhD*
Chestnut Health Systems	*University of Illinois Chicago*
221 W. Walton St. Chicago, IL	1040 W. Harrison St. Chicago, IL
312-274-5316	312-996-8560
dpwatson@chestnut.org	*jaswartz@uic.edu*

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB), which will include local experts on treatment for opioid use disorder, specifically medications for opioid use disorder (MOUD).

The DSMB will meet quarterly to ensure participant safety and review study conduct and progress. They will (a) review research protocols and plans for data safety and monitoring; (b) review clinical trial progress, including data analysis quality and timeliness, subject recruitment, subject risk versus benefit, and other factors that may influence outcomes; (c) review serious adverse event reports and provide feedback and oversight they are reported properly to the appropriate Institutional Review Boards (IRB) and the Office of Human Research Protections (OHRP); (d) make determinations as to whether the study should be continued, changed, or terminated based on the data. An analysis of key variables at each of our administrative data pulls will be reviewed for any significant negative outcomes that might result from participation in the POINT arm.

Data Safety Monitoring Board Members:

- Juleigh Nowinski-Konchak; Addiction Medicine and Public Health Physician, Cook County Health
- Brad Ray; Associate Professor, Wayne State University; Director, Center for Behavioral Health and Justice.
- Karla Wagner; Associate Professor, University of Nevada Reno

10.1.7 CLINICAL MONITORING

Not applicable.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The project manager and principal investigators will perform internal quality management of study conduct, data and specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- The project manager will review the documentation of the consenting process with a subset of participant enrollments (as described in Section 6.2.1. Interventionist Training and Tracking), and all completed consent documents will be reviewed. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Electronic data --- Data will be entered directly into the study database. To ensure accuracy completeness, records will be reviewed by the project manager. Data checks will also be conducted by the principal investigator. The process of data collection will be reviewed by the project manager with a subset of enrollments (as described in Section 6.2.1. Interventionist Training and Tracking).

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study by the project manager and principal investigator. Procedures for ensuring fidelity of intervention delivery are also described in Section 6.2.1, Interventionist Training and Tracking.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the research assistants at the site under the supervision of the project manager and principal investigator. Original data will be entered directly into the REDCap data collection system, which is accessible by team members only and can be immediately reviewed by the project manager. The research assistants will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported, and the project manager will review each electronic record.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Hardcopies of the enrollment documents (consent form, competency questions, and health information release forms) will be kept for each participant consented/enrolled in the study. Each document will also be scanned and electronically uploaded to a secure Box Health folder so that they can be reviewed for completeness.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for 3 years after the final patient is enrolled.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol or International Council on Harmonisation Good Clinical Practice (ICH GCP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly. These practices are consistent with ICH GCP:

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

It will be the responsibility of the principal investigator to use continuous vigilance to identify and report deviations. All major deviations will be reported to the IRB promptly, within 5 business days. Minor protocol deviations will be reported at the time of the subsequent IRB renewal or closure.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. A limited data set with all identifiers removed may be requested from researchers. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore,

persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
CC	Control Condition
CFR	Code of Federal Regulations
COC	Certificate of Confidentiality
COIP	Community Outreach & Intervention Projects
CONSORT	Consolidated Standards of Reporting Trials
COVID	Coronavirus Disease
DSMB	Data Safety Monitoring Board
FQHC	Federally Qualified Health Center
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICH	International Council on Harmonisation
IRB	Institutional Review Board
ITT	Intention-To-Treat
MSHC	Mile Square Health Center
MOUD	Medications for Opioid Use Disorder
MRN	Medical Record Number
NCT	National Clinical Trial
NIH	National Institutes of Health
OUD	Opioid Use Disorder
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SOA	Schedule of Activities
SSP	Syringe Service Program
STAMINA	Syringe Service Telemedicine Access for Medication-Assisted Intervention through Navigation
TC	Treatment Condition
UP	Unanticipated Problem
UIC	University of Illinois Chicago
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2	7/20/2020	The "Follow-Up Contact Information Card" was removed from the protocols and replaced with a "Client Contact and Locator" information form was added to the enrollment procedures. Chestnut Health research staff will also review this form via telephone with each participant during the baseline visit. Questions concerning comfort levels of different appointment modalities were added to baseline data collection. UI Health Medical Record Number (MRN) has been added as a recorded variable to baseline data collection. Protocols were amended to permit research staff, rather than only COIP staff, to schedule MOUD appointments for the control arm participants.	Chestnut Health research staff will now be responsible for scheduling all follow-up interviews and additional contact information is being collected to assist with these processes. Due to COVID-19, telemedicine appointments are more common and accepted. Thus, we want to measure participants' comfort associated with different modalities. The MRN will permit research staff to obtain administrative MOUD treatment data. Research staff will schedule appointments to improve the client flow and decrease confusion.
3	8/10/2020	SSN has been added as a recorded variable to baseline data collection. The inclusion criteria were amended to require participants to reside in Cook County, IL. The exclusion criteria were amended to require participants not to have plans to move outside of Cook County, IL in the next 6 months or have to serve a criminal sentence in the next 6 months. The follow-up data collection location was amended from Lighthouse Institute to COIP field sites.	The SSN will assist with locating participants for follow-up. The use of the last 4 will also be necessary for obtaining administrative records. The eligibility criteria were amended to increase the likelihood that participants are accessible for follow-up interviews. The follow-up data collection was amended because Lighthouse Institute no longer permits in-person interactions due to COVID-19.

		The payment form was amended from cash to VISA gift card and clarified that the $35 follow-up payment includes $25 for the interview and $10 for the drug screen. Additional COVID-19-related disclaimers were added to the consent form that permit changes to the follow-up data collection.	The payment form and breakdown clarification were amended to permit telephone data collection, without drug screen, due to COVID-19.
4	08/25/2020	The eligibility screener for opioid withdrawal was changed from the Subjective Opioid Withdrawal Scale (SOWS) to the Clinical Opioid Withdrawal Scale (COWS), with the "extreme" range still being excluded and offered immediate treatment.	The screener amendment was a result of advice from the clinical team at MOUD treatment provider. The providers indicated the COWS provides better accuracy.
5	09/09/2020	Block randomization was added to our protocols (i.e., one block for people interested solely in methadone treatment, one block for people open to any medication). Family Guidance was added to the list of administrative data sources.	The block randomization will permit us to examine the two sets of participants individually, if needed, given that the treatment linkage for methadone and suboxone/vivitrol is different. Family Guidance was added to the list of administrative data sources because Mile Square has not yet been able to offer methadone due to COVID-19 related delays in the approval process.
6	10/14/2020	A "Consent to Contact" form was added to our recruitment protocols.	The form permits us to gather someone's contact information if they indicate interest and schedule them for a time that works for their schedule or when they are ready for treatment.
7	1/11/2021	The consent form was amended to more clearly describe the duration of baseline activities. The "Consent Competency Checklist" was also amended to include a	The consent form and "Competency Checklist" amendments aim to ensure participants understand the length of the baseline activities and encourages enrollments

		question on how long the baseline activities take. The consent form was amended to request permission to audio record the discussion between research staff and participants regarding their preferred medication. Further permissions are requested to use the audio recording as data for the study.	only by those who have the time to complete all activities. The audio recording of the MOUD discussion will be used for quality assurance to ensure research staff explain the medications accurately. The addition of the research data permission will provide insight on client opinions on the different medications.
8	4/22/2021	The drug screen type at the follow-up interview was amended from saliva to urine. The 6-month follow-up interview was eliminated. The recruitment protocols were amended to include assistance from a company that provides specialized study recruitment. The consent form was amended to request permission to obtain a picture of participants for locating purposes only.	The drug screen type was amended because the urine screen provides better accuracy. Due to slow enrollment, the removal of the 6-month interview will allow for an extended recruitment period. The addition of the recruitment company assistance is also to improve enrollment rates. The photo of participants will be used to improve tracking abilities and increase rates of follow-up interviews.
9	5/17/2021	The saliva drug screen at baseline has been eliminated (leaving only the urine drug screen at both time points). The consent form was amended to better explain possible costs associated with treatment.	The removal of the saliva drug screen occurred because the tests proved to be unreliable and challenging to use. The consent form was amended to ensure that participants understand that there are possible costs associated with treatment should they decide to receive treatment outside of Mile Square, which is an FQHC and has the ability to assist patients in applying for

			insurance and covering treatment costs.
10	6/24/2021	The baseline incentive amount was increased from $25 to $50. The recruitment protocols were amended to include assistance from a Lighthouse Institute outreach. Questions from the baseline and follow-up questionnaires were removed to shorten the interview length.	The baseline interview is more intensive and time-consuming than the follow-up interview, and feedback from participants indicated that the discrepancy in payment between baseline ($25) and follow-up ($35) was unfair. [Note: All previously consented participants will be offered the compensation difference.] The addition of the outreach team is to improve enrollment rates. Unnecessary questions were removed from the instruments to decrease the time burden on participants.
11	2/17/2022	The eligibility assessment was amended to include the urine drug screen, which was previously only used during data collection.	Implementing the drug screen during the eligibility assessment allowed for confirmation that participants are not already prescribed MOUD at enrollment.

11 REFERENCES

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