# Project POINT:
# Effectiveness and Scalability of an Overdose Survivor Intervention

**Protocol Number: 1706859955**

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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 Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as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 National Institute on Drug Abuse 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 ICH GCP Training.

The protocol, informed consent form(s), 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(s) 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(s) 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: 02/03/2020

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Title*: Principal Investigator

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# 1 PROTOCOL SUMMARY

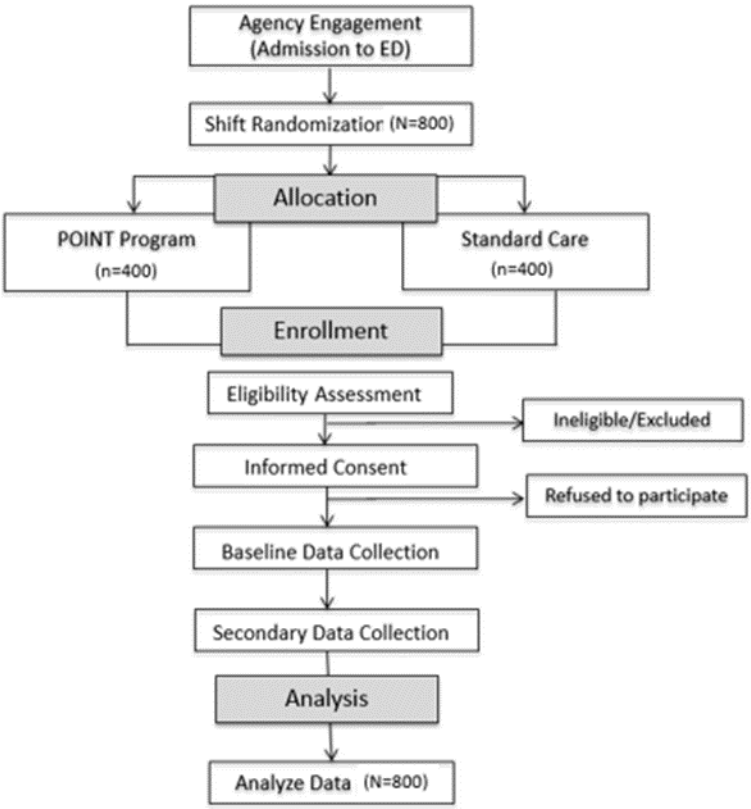
## 1.1 SYNOPSIS

| | |
|---|---|
| **Title:** | Following Opioid Overdose Survivors to Improve Emergency Department-Based Services: A Pilot Study |
| **Grant Number:** | R33DA045850 |
| **Study Description:** | The investigators seek to conduct a pragmatic trial to assess the effectiveness of Project POINT (Planned Outreach, Intervention, Naloxone, and Treatment), an emergency department (ED)-based peer recovery coach intervention for people with opioid use disorder who present to the ED. |
| **Objectives*:** | The primary goal of this project is the establishment of POINT as an effective and scalable intervention for connecting patients to medications for opioid use disorder (MOUD). This study employs a Hybrid Type 1 effectiveness implementation design to take full advantage of current POINT expansion efforts currently happening in Indiana, with the goal of the effectiveness component described in this protocol to be testing the effectiveness of POINT under real-world conditions. |
| **Endpoints*:** | Primary Outcome Measure:<br>1. Overdose Admissions<br>Secondary Outcomes Measures:<br>2. Medication for opioid use disorder (MOUD) engagement<br>3. Duration of MOUD Engagement<br>4. ED Admissions<br>5. Inpatient Hospital Admissions<br>6. Time to Relapse<br>7. Medicaid Enrollment for Participants Without Insurance<br>8. Child Welfare Involvement<br>9. Incarceration |
| **Study Population:** | Inclusion Criteria: (a) Revived from a drug overdose or admitted to the ED for an opioid-related health issue, including opioid withdrawal, abscess (from intravenous (IV) opioid use), endocarditis (from IV opioid use), or active opioid intoxication; (b) Score at least "1" on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 for Opioid Use Disorder screening tool; (c) Eligible for discharge from a participating ED and deemed able to speak to research staff by ED staff; (d) Be 18 or older; (e) Be medically stable (i.e., cleared to leave the ED by a physician) and capable of providing consent. |
| **Phase* or Stage:** | N/A |
| **Description of Sites/Facilities Enrolling Participants:** | Indiana University (IU) Health Ball Memorial Hospital; IU Health Methodist Hospital |

| | |
|---|---|
| **Description of Study Intervention/Experimental Manipulation:** | POINT is a quality improvement initiative that connects trained outreach workers with ED patients who experienced a non-fatal overdose. A member of the POINT team (a peer recovery coach) meets patients after they have experienced an opioid overdose and, following a model of patient-centered care, offers them a range of evidence-based services including a brief assessment of high-risk behaviors, Hepatitis C and HIV testing, harm reduction counseling informed by motivational interviewing, and treatment referrals with follow-up to either MOUD provider, detoxification services, or an inpatient treatment setting. |
| **Study Duration*:** | 58 months (February 2018-December 2022) |
| **Participant Duration:** | Original data collection occurs only at enrollment and includes a single 30–60-minute structured interview. Administrative data is accessed for a 5-year period (i.e., 3 years prior to enrollment- 2 years post enrollment). |

## 1.2 SCHEMA

***Figure 1: Flow Diagram including original planned enrollment****




Note: Planned enrollment was not met after enrollment activities were temporarily stopped for several months at the busiest enrollment site due to the COVID-19 pandemic. An alternative plan using a retrospective case control design was approved by the study funder.

### 1.3 SCHEDULE OF ACTIVITIES

**Table 1: Schedule of Activities**

| ***Procedures*** | ***Enrollment*** | ***24 months post-enrollment*** |
|---|---|---|
| Informed Consent | *x* | |
| Intake Information | *x* | |
| Patient Questionnaire | *x* | |
| Adverse Childhood Experiences (ACEs) Questionnaire | *x* | |
| Secondary Data Pull | | *x** |
| *Secondary data are pulled at a coordinated time point at which data reflecting 24 months post-enrollment was provided for each study participant. | | |

## 2 INTRODUCTION

### 2.1 STUDY RATIONALE

Opioid misuse and addiction are at historic heights in the United States. Despite significant need, substantial treatment and design barriers prevent many opioid users from accessing medications for opioid use disorder (MOUD), the gold standard treatment for opioid use disorder (OUD).

Planned Outreach, Intervention, Naloxone, and Treatment (POINT) is an emergency department (ED)-based intervention for engaging opioid overdose survivors into MOUD. POINT was conceptualized (and implemented at its originating site) as a critical time intervention in that it seeks to quickly mobilize support for members of a highly vulnerable population at a juncture in their lives when they are likely to be receptive to assistance (i.e., after an overdose). It accomplishes this through use of peer recovery coaches (i.e., individuals with lived experience of recovery who are trained to assist those struggling with addiction) who assist patients to navigate barriers to MOUD access after ED discharge. The use of recovery coaches in substance use disorder services is based in the premise that patients will be more receptive to sharing their personal struggles with someone who has had similar experiences. The primary goal of this project is the establishment of POINT as an effective and scalable intervention for engaging patients in MOUD through a Hybrid Type I effectiveness-implementation study. The component of this study described in this protocol is a pragmatic trial that seeks to understand the effectiveness of POINT under real-world conditions.

### 2.2 BACKGROUND

Despite its demonstrated effectiveness, the availability of providers offering MOUD is in short supply. Even where MOUD is available, a significant portion of opioid users encounter treatment and design barriers. Moreover, stigma associated with OUD and ubiquitous abstinence-only views have resulted in political roadblocks to MOUD expansion and reluctance among opioid users to seek and accept treatment. Previous studies indicate high motivation for change among opioid users, suggesting treatment avoidance is not the primary issue. As such, an increase in MOUD availability must be accompanied by innovative

approaches to help opioid users navigate obstacles blocking both access to and continued engagement in MOUD. Furthermore, people who use opioids and injection drugs inconsistently utilize health care services and are heavier users of emergency and inpatient hospital care than the general population. Therefore, the ED is in a unique position to identify, develop, and implement solutions to improve outcomes in this population. There is indeed burgeoning evidence supporting ED-based interventions for substance misuse.

At the time of this study's conceptualization, POINT was developed and operating in Indianapolis's Eskenazi Hospital. Initial results of a quality improvement study supported the intervention's potential for improving patient outcomes. The proposed project aimed to extend this work

Using settings and protocols more reflective of "real-world" conditions to study POINT will help ensure relevance of resulting findings to practice. This is particularly important considering the need for fast translation of evidence in light of the significant toll the opioid crisis is taking on the nation. The fact that POINT was already undergoing scaling activities at the time of the study's conceptualization was an important opportunity to take advantage of considering key stakeholder decisions to promote or adopt interventions are often made without regard to the scientific evidence.

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 KNOWN POTENTIAL RISKS

Immediate risks to participants include: the potential that individuals may feel uncomfortable due to the sensitive nature of some of the questions that will be asked at intake or that they may become fatigued answering questions. There is also a risk of loss of confidentiality related to data collection, including the secondary data collection, should there be a breach during the collection or data transfer process (prior to the deidentification of data). In particular, individuals may be identified as a substance user. This may result in stigma for the individual. However, it is important to note that individuals will not suffer risk of criminal prosecution for drug use should their opioid overdose become known by the police, as possession, not use, is a criminally prosecutable risk in Indiana.

### 2.3.2 KNOWN POTENTIAL BENEFITS

Immediate benefits that subjects may likely gain include: the opportunity to discuss and reflect on their recent opioid use and/or overdose, a list of resources that may benefit them as someone who uses opioids (these resources will be provided even if they do not choose to participate in the study), and the opportunity to inform research that may lead to the development of stronger interventions to assist people at risk of future opioid use or overdose.

### 2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Sensitive data collected for this study (e.g., data pertaining to illicit drug use) are necessary to assess the proposed outcomes and examine the implementation of POINT. Study procedures aim to minimize risks associated with the collection of these data through the following ways: (a) all original data collection

will occur in a private area where others cannot overhear what is shared or see the interaction between research staff and participant; (b) all data collected during these interviews will be entered directly into Research Electronic Data Capture (REDCap to ensure secure data storage is HIPAA compliant and that only relevant research team members will have access to these data; (c) research staff will assure all participants throughout the interview that they may choose to skip any questions they do not want to answer and will also end the interview or skip the question if the participant seems distressed about sharing the information requested; (d) secondary data will be accessed through the assistance of Regenstrief Institute, an honest broker who can act as a firewall between personally identifiable health data and the researchers. Regenstrief will mask and merge the data and ensure all data are stripped of personally identifying information before delivering them to the research team. Specifically, Regenstrief will link hospital, government, substance abuse treatment, and data collected by the research staff and will keep the identification key and not share it with the research team so that information remains confidential.

## 3 OBJECTIVES AND ENDPOINTS

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS | PUTATIVE MECHANISMS OF ACTION |
|---|---|---|---|
| Primary | | | |
| Assess POINT's effectiveness at reducing overdose presentations to the emergency department. | Overdose Admissions | The primary goal of the intervention as it is designed is to reduce overdoses by linking clients to MOUD treatment. | Engagement in MOUD treatment is demonstrated to reduce overdose. |
| Secondary | | | |
| Assess POINT's effectiveness at improving treatment-related outcomes. | MOUD Engagement | These outcomes should improve following linkage to MOUD. | MOUD treatment is associated with better treatment outcomes compared to alternative treatments for OUD. |
| | Duration of MOUD Engagement | | |
| | Time to Relapse | | |
| | ED Admissions | | |
| | Hospital Admissions | | |
| | Overdose Mortality | | |
| | Medicaid Enrollment | | |
| Exploratory | | | |
| Assess POINT's effectiveness at improving recovery-related outcomes. | Child Welfare System Involvement | These outcomes should improve as a function of treatment engagement. | MOUD treatment should result in greater abstinence from illicit opioids that will improve other areas of a patient's life. |
| | Incarceration | | |

# 4 STUDY DESIGN

## 4.1 OVERALL DESIGN

The primary objective of this pragmatic clinical trial is to replicate POINT at two new hospitals and establish POINT's effectiveness compared to standard care. In doing so, we aim to understand POINT's effect on the recovery process, including treatment and recovery outcomes and overdose. We hypothesize that POINT patients will engage in MOUD at higher rates, remain in treatment longer, and have significantly improved outcomes in comparison to the standard care group.

Hospital patients meeting the eligibility criteria at one of the two participating EDs are approached by a recovery coach or research assistant and invited to enroll in the study. Participants of the study are randomly enrolled into one of two study arms: (1) the POINT intervention arm, in which they receive ongoing recovery support services from a recovery coach or (2) the control arm, in which they receive a list of available local resources for substance use disorder from the research assistant. The study utilizes shift-level randomization, and each day of enrollment is separated into three enrollment shifts which are randomly assigned to one of the two study arms. Thus, participants' arm assignment is pre-determined by the shift in which they are discharged from the ED and enrolled into the study. Participants are asked to complete a single structured interview at the time of their enrollment and are followed longitudinally only through administrative data, which is collected for participants from three years prior to their enrollment through two years following their enrollment.

## 4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The rational for a pragmatic trial is based on the fact that POINT was already demonstrating success and implemented as standard care at its originating hospital site and was under consideration to be implemented as regular care at the current study's participating hospital system at the time of study design. Given this, a standard explanatory trial was considered unfeasible. Furthermore, the funding mechanism supporting the project was designed to support research aimed at taking advantage of opioid use disorder-related initiatives that were already underway as part of Opioid State Targeted Response funding, which required researchers to design a study around already developing state plans and efforts.

## 4.3 JUSTIFICATION FOR INTERVENTION

The rational for providing recovery coach support at the patient ED bedside is because an emergency room encounter is considered a critical point in time when a person might be more motivated toward and accepting of treatment linkage. The minimal acceptable participation is engagement with the recovery coach at one time point while in the emergency department.

## 4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment. The end of the study is defined as completion of this assessment.

# 5 STUDY POPULATION

## 5.1 INCLUSION CRITERIA

To be eligible for the study, a patient must:

1. Be revived from a drug overdose or admitted to the ED for an opioid-related health issue, including opioid withdrawal, abscess (from IV opioid use), endocarditis (from IV opioid use), or active opioid intoxication.
2. Score at least "1" on the opioid use disorder screening tool.
3. Be eligible for discharge from one of the two participating EDs and deemed able to speak to research staff by ED staff.
4. Be age 18 or older.
5. Be medically stable (i.e., cleared to leave the ED by a physician) and capable of providing consent.

## 5.2 EXCLUSION CRITERIA

A patient will be excluded from the study if:

1. They are unable to answer the 3 study competency questions that indicate capability of providing consent.

## 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 or recovery coaches learn that the clinical information provided for someone previously consented to the study was inaccurate (for example, if a research staff member learns from a participant during their baseline assessment that their admission to the ED was non-opioid related and that the participant does not use opioids), 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

Individuals who are admitted to the ED for either an opioid overdose OR an opioid-related health issue will be deemed initially eligible, and the research personnel will be alerted of their presence in the ED. Research staff will also verify that the patient is at least 18 years of age. Once the initial eligibility is determined per the medical staff (reason for admission and at least age 18), either the recovery coach or the research assistant will approach the patient to inform them of study. This interaction will occur in the room in which they are receiving care in the ED, which is confidential area of the ED. They will use this initial meeting to explain the study and to ask the patient the questions from the opioid use disorder screening tool. If the patient scores at least a "1" on the opioid use disorder screening tool, they will be initially eligible for the study. They will then provide a brief overview of who they are and what the POINT study involves.

Because this initial interaction will occur prior to their discharge clearance, the research staff or recovery coach will reiterate to the patient that the research study is not a part of the treatment plan, and the patient may decline the study without impacting their treatment. Further, this "pre-discharge clearance" interaction will not hinder the discharge process; rather, we will utilize the "down time" the patient experiences while waiting in the ED. Once this initial discussion is complete, and if the patient chooses to take part, the research staff will return to the patient once he or she has received medical clearance for discharge from the ED and will move forward with the consent process.

Participants receive a $30 gift card for their participation in the study. Research staff or recovery coaches will inform patients of this while explaining the study to the patient. The incentive is received at the end of their study visit.

Retention strategies are not applicable to the study, as participant will only be followed longitudinally through secondary administrative data.

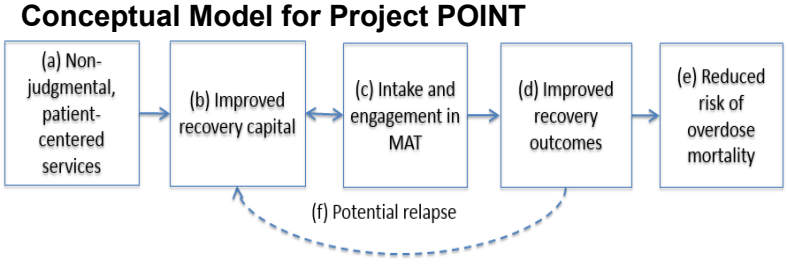
# 6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

## 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.

The POINT intervention utilizes the services of a recovery coach (i.e., someone certified by the Indiana Counselors' Association on Alcohol and Drug Abuse to deliver recovery supports who has lived experience with addiction). The recovery coach meets patients in the ED after they have been revived from an overdose or are admitted to the ED for an opioid-related health issue, including opioid withdrawal, abscess (from IV opioid use), endocarditis (from IV opioid use), or active opioid intoxication. The



recovery coach offers the patient a range of evidence-based services including a brief assessment of high-risk behaviors, Hepatitis C and HIV testing, harm reduction counseling informed by motivational interviewing, and treatment referrals with follow-up to either a MOUD provider, detoxification services, or an inpatient treatment setting—with most patients choosing MOUD referral. Patients are also offered a take-home naloxone kit (i.e., the overdose reversing drug, which is offered as part care delivered by the recovery coach) and assistance with Medicaid enrollment, if applicable. Close collaboration with the local community mental health provider ensures POINT patients have their first assessment for MOUD within 1-2 business days of ED discharge.

Grounded in the concept of critical time intervention, recovery coaches provide over the phone or in person support to navigate barriers to care throughout the recovery process. Recovery coaches also offer to accompany patients to intake appointments or criminal justice and child welfare meetings as part of the standard care they deliver. Recovery coaches reach out to the client every 2-3 days, initially, until the patient is successfully engaged in recovery services. The entire care transition process takes between 2 weeks and several months, and POINT leaves the door open so patients can re-engage at any point they require help overcoming recovery barriers. Recovery coaches do not collect data for study purposes during this time; rather, any information they collect will be solely for the purposes of providing professional care as a recovery coach.

The control condition refers to standard care within the ED, in which patients receive a list of available local treatment options for opioid use disorder.

### 6.1.2 ADMINISTRATION AND/OR DOSING

The POINT intervention begins immediately following enrollment, at which point the recovery coach begins speaking with the participant about recovery support services. Depending on the needs and desires of the client, the recovery coach customizes the delivery of his or her services to aid the participant in getting the resources they need to support recovery. Once the participant leaves the hospital, the recovery coaches attempt to remain in contact and reaches out to the participant every 2-3 days initially or until the patient is successfully engaged in recovery services. The process will depend on the client's interest and engagement, but the recovery coach often works with them for a period of weeks or months. POINT recovery coaches intentionally make room for open communication and re-engagement so patients can ask for help overcoming recovery barriers.

Following the patient's exit from the hospital, the recovery coach attempts to make additional contact. If recovery coaches are unable to immediately reach the patient, they complete the following steps.

- They continue to attempt follow-up calls, emails, texts for 2 weeks. The number provided could belong to another individual or be temporarily or permanently out-of-service or disconnected. The recovery coach will continue to follow-up, as the phone status might change, and make an attempt to call each person at least once a day during the 2-week time period.
- After two weeks, the recovery coach will stop trying to engage the patient. If the recovery coach has the opportunity to send an email or text or leave a voice mail, they will inform them the participant they are going to stop trying to call them but give them their contact information if they decide they need assistance with anything.
- If they reach an individual aside from the patient (e.g., mom, dad, spouse), the recovery coach will state that they are calling from IU Health and that they are attempting to reach the patient's name. No details of the study or the context of call will be provided to the individual.

If the recovery coach is able to reach the patient, and the patient indicates they want services, the recovery coach will provide individualized services while considering the following.

- The recovery coach will make sure all recovery avenues are open to the client such as medication for opioid use disorder (MOUD) (e.g., ensuring they are aware of methadone, Suboxone, and Vivitrol availability) and abstinence-based treatment.
- The recovery coach will discuss the evidence, benefits, and drawback of each type of treatment with the patient.
- The recovery coach will make sure the right resources are in place when connecting the patient to care, including payment source, insurance, and transportation.
- The recovery coach should continue to provide personalized support based on the needs of the patient.

POINT uses a warm handoff model, which means that recovery coaches:

- work to link patients to appropriate substance use disorder treatment and recovery supports,
- should obtain a health information release from the provider to which the patient is referred, and it should cover 12 months,
- continue to follow-up with the patient after they are connected to other supports for anywhere from 2 weeks to 3 months, depending on the patients' level of need and comfort with the services they were linked to, and
- allow patients to reengage with POINT services at any time for any reason if they need support in their recovery.

## 6.2 FIDELITY

### 6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Fidelity assessments with the recovery coaches and hospital sites will ensure compliance with the POINT intervention design. A checklist of putative critical intervention components will guide the fidelity audit and feedback activities. We will conduct site visits at pre-implementation, early implementation (1 month following kick-off), mid-implementation (approximately 3 months), and late implementation (6 months). The day-long site visits will include interviews with clinicians and administrators, observation of POINT intervention, and review of records.

## 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The study is randomized at the enrollment shift level. Each day of study enrollment is broken into three shifts (8am-3:59pm, 4pm-11:59pm, 12am-7:59am). In advance, each shift is randomly assigned to one of the two enrollments arms (i.e., POINT or control) to determine whether patients discharged during these times will enroll into the POINT arm or the standard care arm. Any individual who is cleared for discharge from the ED for an overdose or for an opioid-related health issue, including opioid withdrawal, abscess (from IV drug use) or active opioid intoxication will be eligible for the study. As determined by the preset randomization, recovery coaches (RC) will engage with patients cleared for discharged from the ED during the POINT shifts and research assistants (RA) will engage with patients cleared for discharged from the ED during control shifts.

Additional note: The study sites plan to implement Project POINT regardless of the research study. We are not modifying any aspect of POINT for the study purposes. Therefore, all recovery coach duties

(baseline administrative data collection, provision of naloxone, patient follow-up) are part of POINT prescribed services that would be carried out regardless of the research. We are randomizing the shift POINT is delivered on to take advantage of the fact that they are not able to fully staff all hospital shifts with a recovery coach--thus allowing us to test the intervention's effectiveness. Only those patients in the standard care arm will be asked to complete data collection activities that would not be completed outside of the research study.

| **Sample randomization for week of services** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Week** | **Shift** | **Day** | | | | | | |
| | | **Mon** | **Tue** | **Wed** | **Thu** | **Fri** | **Sat** | **Sun** |
| 1 | 8am-3:59pm | RC | RA | RA | RC | RC | RC | RA |
| | 4pm-11:59am | RA | RC | RC | RA | RA | RA | RC |
| | 12am-7:59am | RC | RA | RA | RC | RA | RA | RC |

## 6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Not applicable; participants of the POINT intervention or not required to adhere to any protocol.

## 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

If a participant wishes to withdraw from the study, they can notify the Principal Investigators, Research Assistants, or Peer Recovery Coaches at any time. While there are no follow-up data collection activities with participants, participants are provided with the contact information for a Principal Investigator and the IRB and informed that they can make contact at any time to withdraw. Withdrawal from the study will not adversely affect the participant. If the participant is receiving POINT services, they will have the option to continue receiving them if they withdraw from the study. Should a participant withdraw, we will remove their data from the sample.

## 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study if the participant is later determined to not have originally met the inclusion criteria (e.g., admitted for an opioid-related reason). Subjects who have signed the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will remain eligible to continue receiving recovery coach services.

### 7.3 LOST TO FOLLOW-UP

Study participants are involved in data collection activities at a single time (i.e., enrollment) and do not participate in any follow-up data collection. Participants of the intervention arm are not required to engage in further interactions with the recovery coach; thus, participants can disengage whenever they prefer.

## 8 STUDY ASSESSMENTS AND PROCEDURES

### 8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

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

Prior to recruitment, a research assistant or recovery coach will (a) verify that patients are at least 18 years of age and (b) have been admitted to the ED for an opioid-related reason. Additionally, prior to screening the patient for eligibility, it must be confirmed that (c) a patient is cleared for discharge from the ED by a healthcare provider; this may include patients who are discharged from the ED but admitted to inpatient care and those returning home. To do so, the research assistant or recovery coach will first approach the ED staff and ask if the patient is medically cleared for discharge. If so, the patient may be approached by the study team member.

Subsequently, the research assistant or recovery coach will utilize a recruitment script to introduce themselves and the study and (d) assess the patient for an opioid use disorder by reading the questions from the *DSM-5 Criteria for Diagnosis of Opioid Use Disorder* to the patient. A score of at least "1" is required for eligibility. Lastly, they will read the statement of informed consent to the participant if they are interested in the study and will confirm the final component of eligibility by (e) reading three questions to the patient to confirm the patient's competency: (1) Can you repeat to me the purpose of the study? [Response: The patient must say something indicating they know we are interested in studying opioid use and/or overdose.] (2) Do you remember some of the types of data we will be collecting about you or the agencies we will be getting them from? [Response: The patient must name at least two data sources.] (3) Do you remember what you should do if you decided you no longer wish to take part in the study after leaving here? [Response: The patient must indicate that they can call the research team or IRB and let them know.] If the patient does not answer correctly, the research team member will attempt to re-explain the consent form and ask the questions a second time. If the patient still does not answer correctly, the patient is not eligible for the study.

If the patient meets all criteria and consents to enrollment, the patient will be asked to immediately complete a structured interview that asks questions regarding the patient's:

1. Demographics

2. Social support
3. Living arrangements
4. Drug use
5. Context of current overdose or ED admission
6. Treatment history
7. Interest in recovery services
8. Use of strategies to reduce risks related to drug use
9. HIV and Hepatitis C
10. Physical and mental health

The patient will also be asked to complete the Adverse Childhood Experiences questionnaire.

In addition to the original data collection, administrative data will be collected for each participant to assess long-term impacts regarding health, treatment, criminal justice, and child welfare involvement, as well as death records. Secondary data collection for the study will be assessed accessed from the following sources for three years prior to a participant's enrollment through two years following:

1. Indiana Network for Patient Care (*hospital and overdose admissions data*)
2. Indiana Scheduled Prescription Electronic Collection & Tracking Program (INSPECT) (*prescription information for controlled substances*)
3. Division of Mental Health and Addiction (*methadone treatment information*)
4. Indiana Office of Medicaid Planning and Policy (*Medicaid enrollment information*)
5. Indiana Department of Child Services (*child welfare involvement information*)
6. Publicly available arrest and incarceration data via (a) Indiana Department of Correction's prison incarceration search portal and (b) Marion County's inmate database search portal
7. Indiana Department of Public Health Vital Records Data (*state health/vital records*)

## 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***.

These will include the following as pertains to the study: violation of confidentiality; discomfort due to interview procedures (including embarrassment in disclosing sensitive information); and disclosure of information about current or intended physical harm to self or others.

### 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.

These will include the following: death; subsequent hospitalizations; and any other conditions or situations members of the DSMB believe represent serious adverse events that can be measured with the available data.

### 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

As defined in 8.3.4, assessment of adverse events from study data will not occur until after the participant is finished participating in the intervention. This is because all outcome data will come from secondary datasets collected at the end of the study. All adverse events that will be measured using these data (e.g., ED encounters, hospital admissions, overdose, and overdose and all-cause mortality) are expected due to the nature of opioid use disorder. Should an adverse event be reported to the researchers outside of secondary data sources, a clinician with appropriate expertise in opioid use disorder will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

### 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) for participants receiving the POINT intervention may come to the attention of recovery coaches while performing follow-up engagement. However, the study relies on administrative data to follow participants longitudinally and does not allow study personnel to assess for adverse events in real-time.

### 8.3.5 ADVERSE EVENT REPORTING

Adverse events will be reported to the IRB and the NIDA Program Officer in regular annual reporting.

#### 8.3.6 SERIOUS ADVERSE EVENT REPORTING

Serious adverse events will be reported to the IRB and NIDA Program Officer within 24 hours, and a written follow-up (including information on the date of the event, what occurred, actions taken by project staff, any planned follow up, the intervention group/study arm of the affected participant, whether the event appears to be related to the intervention) will be provided within 72 hours of the event. Confidentiality will be breached in any circumstance where mandatory reporting is required. We have put procedures in place with the social work staff at the hospital and will inform them when there are concerns of self-harm or child abuse/neglect. As this is a long-term follow-up study, we have no way of tracking a number of events that could happen.

If any adverse event is noted, we will immediately contact the IRB and inform the ED. Additionally, participant withdrawals or complaints will be monitored by Dr. Watson to ensure that study procedures have not resulted in unanticipated outcomes to participants. Results of all data safety and monitoring activities will be reported to NIDA annually. 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.

#### 8.3.7 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 Endpoint:

- Overdose Admissions
  - [Measured: 1 year pre-enrollment through 1 year post-enrollment]

We hypothesize that, compared to patients in the control condition, patients receiving the POINT intervention will experience fewer subsequent admissions to the ED for overdose.

Secondary Endpoints:

- MOUD Engagement
  - [Measured: 1 year pre-enrollment through 1 year post-enrollment]
- Duration of MOUD Engagement
  - [Measured: 1 year pre-enrollment through 1 year post-enrollment]
- ED Admissions
  - [Measured: 1 year pre-enrollment through 1 year post-enrollment]
- Inpatient Hospital Admissions
  - [Measured: 1 year pre-enrollment through 1 year post-enrollment]
- Time to Relapse
  - [Measured: Enrollment through 1 year post-enrollment]
- Medicaid Enrollment for Participants Without Insurance
  - [Measured: Enrollment through 1 year post-enrollment]
- Child Welfare Involvement
  - [Measured: 3 years pre-enrollment through 1 year post-enrollment]
- Incarceration
  - [Measured: 3 years pre-enrollment through 1 year post-enrollment]

We hypothesize that, compared to patients in the control condition, patients receiving the POINT intervention will experience better recovery outcomes (i.e., higher MOUD engagement and longer duration of engagement, lower ED and inpatient admissions, longer times between relapse, higher Medicaid enrollment for those without insurance, lower child welfare involvement, and lower incarceration).

## 9.2 SAMPLE SIZE DETERMINATION

Our goal is to obtain a total of 356 patients in each study arm (n = 712) by Month 32, which will provide us with enough patients to obtain a full year of follow-up data to detect a minimum 6% reduction in our primary outcome (subsequent overdose) at 80% power, assuming a 12% rate of subsequent overdose for the standard care arm at the 5% significance level (this is a conservative calculation based on observed subsequent overdose rates at Eskenazi and Indianapolis Emergency Medical Services).

(Note: This goal was not ultimately reached due research activities needed to stop because of the COVID-19 pandemic. Researchers developed an alternative plan to assess outcomes using a retrospective case control design that was approved by the funder. However, all planned analyses were conducted using collected from patients who were enrolled in the trial.)

## 9.3 POPULATIONS FOR ANALYSES

All participants consented to the trial will be included in the analyses.

## 9.4 STATISTICAL ANALYSES

### 9.4.1 GENERAL APPROACH

We will summarize patient characteristics using means and standard deviations for continuous variables and counts and proportions for categorical variables. Initial analysis of outcomes (using data pulled at 9 months) will focus on MOUD engagement one-month post overdose, as all other outcomes will be too distal to observe any meaningful change. This time period is based on our prior POINT experience demonstrating initial engagement tends to happen within 1-2 weeks of overdose. We will focus on immediate outcomes (e.g., treatment engagement, length, dropout). While observed change in more distal outcomes (e.g., subsequent overdose and mortality) is unlikely to be seen in such a short pilot period, we will look at them and, if needed, adjust the benchmark (established based on our experiment at Eskenazi) for the power analysis. Summary of outcome measures will be computed similarly. The 95% confidence intervals of outcome measures for the POINT and standard care arms will be used to estimate the rate of binary outcomes and mean of continuous outcomes.

The primary analysis involves comparison of outcome measures post ED discharge between the POINT and standard care arms. Binary outcome measures (e.g., MOUD engagement and dropout, subsequent overdose, overdose mortality, and all-cause mortality) will be compared between the POINT and standard care arms using the Fisher's exact test. Length of MOUD treatment will be compared using the Wilcoxon rank sum test. Comparison of the length of time to relapse will be conducted using the survival analysis. Time to relapse will be plotted using the Kaplan Meier curve and comparison between the POINT and standard care arms will be performed using the log rank test.

The secondary analysis involves comparing outcome measures pre- and post-ED discharge for POINT patients. Binary outcomes including child welfare involvement will be compared using the McNemar's test and the continuous outcome including the days of incarceration will be compared using the Wilcoxon signed rank test due to the skewness of the data. Additional analyses will be conducted to account for patient characteristics in the comparison between the POINT and standard care arms using logistic regression for binary outcomes, Poisson regression for length of MOUD treatment, and Cox proportional hazards model for time to relapse. For the comparison pre- and post-ED discharge in the POINT arm, generalize estimating equations approach will be performed using logistic regression for Medicaid enrollment and child welfare involvement and Poisson regression for days of incarceration. Hospitals will be included in the models as a fixed effect to account for the potential differences in patient population across hospitals

### 9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

| Questions | Defined/explained |
|---|---|
| Primary endpoint | |
| *Describe how the primary endpoint is calculated, if not readily apparent* | **Change in Overdose Admissions**: Using electronic health records, it is calculated as the total combined number of overdoses resulting in an emergency department presentation within the specified time period. |
| *Describe the scale (nominal/binary/categorical, ordinal, interval); state if it is measured as a single endpoint/summary measure or repeated measure* | binary |
| *Describe the statistical procedure(s) that will be used to analyze the primary endpoint (e.g., multiple regression, repeated measures mixed models, logistic regression, Analysis of Covariance (ANCOVA)). Describe the covariates and factors in the model. Provide a rationale for covariates and how they will be selected to achieve a parsimonious model. If the decision to specify covariates is deferred for the SAP, indicate here.* | Summarized using frequencies and percentages and then compare arms using the Fisher's exact test. |
| *Describe how results of statistical procedure(s) will be presented (e.g., adjusted means (Least-squares means (LSMEANS)) with standard errors, odds ratios with 95% confidence intervals, prevalence rates, number-needed-to-treat)* | Presented using frequencies and percentages |
| *Describe details to check assumptions required for certain types of analyses (e.g., proportional hazards, transformations or, when appropriate, nonparametric tests)* | The nonparametric Fisher's exact test is used to compare the primary endpoint. |
| *Describe the Populations for which the analysis will be conducted, as discussed in **Section 9.3, Populations for Analyses*** | All study participants |
| *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, non-adherence and lost to follow-up* | We do not expect there to be a large amount of missing data due to the use of administrative datasets. However, missing values may occur when subjects die during the specified time period. Sensitivity analysis is performed by excluding subjects who die during the specified time period. |

### 9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

| *Secondary endpoints* | |
|---|---|
| *Note if analysis of secondary endpoint(s) are dependent on findings of primary endpoint* | Analysis of secondary endpoints are not dependent on the findings of primary endpoint. |
| *Describe how each secondary endpoint is calculated, if not readily apparent* | **Change in MOUD Engagement**: Using state methadone treatment data, Medicaid claims data, state prescription drug monitoring data, and electronic health records data to identify whether or not the person engaged in at least one episode of MOUD treatment (methadone, buprenorphine, or naltrexone) within the specified time period.<br><br>**Change in MOUD Engagement Duration**: Using state methadone treatment data, Medicaid claims data, state prescription drug monitoring data, and electronic health records data to calculate the number of days MOUD treatment was received during the specified time period.<br><br>**Change in ED Admissions**: Using electronic health records, it is calculated as the total combined number of all-cause ED presentation within the specified time period.<br><br>**Change in Inpatient Hospital Admissions**: Using electronic health records, it is calculated as the total combined number of all-cause hospital admissions within the specified time period.<br><br>**Time to Relapse**: Using electronic health records data, it is calculated as number of days to the first overdose ED visit or overdose death since the index ED. Subjects who did not experience overdose ED or overdose death are censored at the end of the specified time period or the time of death due to other reasons, whichever occurred first<br><br>**Change in Medicaid Enrollment for Participants Without Insurance**: Using Medicaid claims data to identify Medicaid coverage among participants within the specific time period. |

| | |
|---|---|
| | **Change in Child Welfare Involvement**: Using child welfare data to identify the number of new cases and children removed from the home within the specified time period.<br><br>**Change in Incarceration**: Using public incarceration data to identify the number of days of incarceration within the specific time period. |
| *Describe the scale (nominal/binary/categorical, ordinal, and interval); state if it is measured as a single endpoint/summary measure or repeated measure* | **Change in MOUD Engagement**: binary<br><br>**Change in MOUD Engagement Duration**: Interval/Ratio<br><br>**Change in ED Admissions**: binary<br><br>**Change in Inpatient Hospital Admissions**: binary<br><br>**Time to Relapse**: Interval<br><br>**Change in Medicaid Enrollment for Participants Without Insurance**: Binary<br><br>**Change in Child Welfare Involvement**: binary<br><br>**Change in Incarceration**: Interval |
| *Describe the statistical procedure(s) that will be used to analyze the secondary endpoint (e.g., multiple regression, mediation or moderation analyses, multilevel modeling, MANOVA). Describe the covariates and factors in the model. Provide rationale for covariates and how they will be selected to achieve a parsimonious model. If decision to specify covariates is deferred for the SAP, indicate here.* | We will summarize patient characteristics using means and standard deviations for continuous variables and counts and proportions for categorical variables. The primary analysis involves comparison of outcome measures post ED discharge between the POINT and standard care arms. Binary outcome measures (e.g., MOUD engagement, subsequent overdose, overdose mortality, and all-cause mortality) will be compared between the POINT and standard care arms using the Fisher's exact test. Length of MOUD treatment will be compared using the Wilcoxon rank sum test. Comparison of the length of time to relapse will be conducted using the survival analysis. Time to relapse will be plotted using the Kaplan Meier curve and comparison between the POINT and standard care arms will be performed using the log rank test. |
| *Describe how results of statistical procedure(s) will be presented (e.g., adjusted means (Least- squares means (LSMEANS)) with standard errors or effect size* | For continuous endpoints, we will present the mean and standard deviation or median and interquartile range for each treatment arm. |

| | |
|---|---|
| | Frequency and percentages are presented for binary endpoints. Time to event endpoints are presented using estimated survival probability at the end of the specified time period. |
| *Describe details to check assumptions required for certain types of analyses (e.g., checks on assumptions of normality, transformations or, when appropriate, nonparametric tests)* | Nonparametric tests are used to compare endpoints between treatment arms. Fisher's exact test is used for binary variables, Wilcoxon rank sum test is used for continuous variables, and log-rank test is used for time to event variables. |
| *Describe the Populations for which the analysis will be conducted as discussed in* ***Section 9.3, Populations for Analyses*** | All study participants |
| *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, non-adherence and lost to follow-up* | We do not expect there to be missing data due to the use of administrative datasets. |
| *If there is more than one primary endpoint or more than one analysis of a particular endpoint, state the statistical adjustment used for Type I error criteria or give reasons why it was considered unnecessary* | Not relevant as there is only one primary endpoint and each endpoint is analyzed once. |

### 9.4.4 SAFETY ANALYSES

Not applicable.

### 9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics will be calculated and competed to assess if there are any significant differences between groups.

### 9.4.6 PLANNED INTERIM ANALYSES

Because the availability of data from administrative sources is outside the control of the research team, interim analyses could not be planned for.

### 9.4.7 SUB-GROUP ANALYSES

No sub-group analyses are planned for this study.

### 9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data by measure and time point will not be listed.

### 9.4.9 EXPLORATORY ANALYSES

No exploratory analyses are planned for this study.

# 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 submitted with this protocol: (1) consent form, (2) list of competency questions, (3) health information release form.

#### 10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Once the patient is determined to meet all the initial eligibility criteria, the research team member will begin informed consent. Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be read the document by a recovery coach or research assistant and review the document. The study team member will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants.

We will not fully disclose the purposes of the research to the standard care arm because (1) Methodist Hospital and Ball Memorial were planning on implementing POINT outside of the context of this study and because their ability to staff recovery coaches is limited anyway, we are not creating any disparity in patients ability to access point that would not naturally exist and (2) we are concerned that full disclosure of the purposes would unnecessarily upset the control arm patients who might desire the services after learning of them.

Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participant will sign the informed consent document prior to data collection beginning. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

### 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. If the risks are not associated with POINT intervention recovery coaching services, participants may continue to receive them.

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

Responses to the structured interview questions will be entered by the recovery coach or research assistant into a form housed in REDCap. Only necessary research team members will have access to these data, and all accounts are password protected.

To protect the confidentiality of patients related to the secondary data, we will work with Regenstrief Institute (an honest broker who can act as a firewall between personally identifiable health data and the researchers) to develop a process for masking and merging the data that will ensure all data is stripped of personally identifying information before being delivered to the research team. Regenstrief will link hospital, government, substance abuse treatment, and structured interview data. We will only be asking for data to be delivered at a single time point, so there will be no need to link data longitudinally. Regenstrief will keep a key that will allow them to identify subjects; however, this key will not be shared with the researchers and will be destroyed at conclusion of the study; thus, researchers will never obtain an identifiable data set. The researchers will keep all data on a HIPPA compliant network/server behind a university firewall, and only those individuals who need access to the data will be able to obtain it using their login ID.

To protect confidentiality of all participants, we will assign each participant a subject identification number that will only be connected to the participants' names on a separate REDCap form, which will only be accessible by necessary research team members. We will store all complete informed consent documents in a locked file cabinet in a locked office. When REDCap data are extracted from the system to be sent to Regenstrief, they will be temporarily stored on a secure server behind a university firewall. They will be sent via a secure online sharing system that requires a password for download. Once accessed and downloaded by Regenstrief, these data will be deleted from the secure server. All grant personnel who are involved in the design or conduct of this research will have demonstrated successful completion of human subjects training, specifically Collaborative Institutional Training Initiative (CITI) Program.

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). 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 proceeding, 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

Original data collected for this study will be stored in REDCap; secondary data will be stored on Regenstrief Institute's secure server until it is de-identified and shared with the research team, at which point it will be stored in a secure Box Health folder. After the study is completed, the de-identified, archived data will be available to other researchers upon request.

### 10.1.5 KEY ROLES AND STUDY GOVERNANCE

| **Principal Investigator** | **Principal Investigator** |
|---|---|
| Alan McGuire, PhD | Dennis Watson, PhD |
| Indiana University | Chestnut Health Systems |
| 1481 W. 10th St. (11H) | 221 W Walton St. Chicago, IL 60610 |
| 317-988-5366 | 312-274-5316 |
| abmcguir@iu.edu | dpwatson@chestnut.org |

### 10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB), which includes representation from a person in recovery and a clinician, will carry out the following activities: (1) Review all research protocols and plans for data safety and monitoring. (2) Review clinical trial progress, including data analysis quality and timeliness, subject recruitment, subject risk versus benefit, and other factors that may influence outcomes. (3) 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). (4) Review outcome analyses and reports of related studies to determine whether the study needs to be changed or terminated. (5) Make determinations as to whether the study should be continued, changed, or terminated based on the data. (6) Review proposed study modifications prior to any changes being implemented by the research team. (7) Protect data confidentiality and review results of monitoring. (8) Determine whether and to whom outcomes should be reported prior to final reporting of study results. (9) Provide reports summarizing findings of DSMB meetings, which will be sent to the appropriate IRBs and NIH staff (if warranted). 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:**

• Danielle McCarthy, MD, Assistant Professor, Department of Emergency Medicine, Northwestern University; expertise in emergency medicine

• Ross Silverman, JD, MPH, Professor, Department of Health Policy and Management, Indiana University-Purdue University Indianapolis; expertise in public health law and ethics

• Antonio (Dave) Jimenez, PhD., Director, Community Intervention Projects, University of Illinois at Chicago; expertise in recovery support services for people with opioid use disorder, experience with clinical trials in opioid using population

• Gina Fears, Certified Peer Recovery Coach, Public Advocates for Community Re-Entry; person with lived experience

### 10.1.7 CLINICAL MONITORING

Not applicable.

### 10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

In addition to required CITI trainings, to ensure adherence to research protocols, the principal investigator and project manager will conduct a required training for all study personnel involved in the enrollment and data collection processes. During this training, the PI and project manager will provide a detailed overview of the study purpose and the enrollment procedures, including the eligibility criteria, screening process, enrollment script, and informed consent procedures. They will also discuss the data collection procedures in detail, during which they will read through the data collection questionnaire and complete mock interviews with study personnel. Subsequently, during the first two weeks of study enrollment, the PI, project manager, or senior research staff will shadow all study personnel during consent and data collection activities to ensure protocol adherence.

Throughout the course of the study, the project manager will monitor enrollment adherence using the Emergency Medical Services (EMS) Patient Tracker system. The system will send daily automated reports to the project manager to indicate which EMS runs involving naloxone administration were taken to the hospitals involved in the study. The project manager will then look up the names of the patients who received naloxone and compare these names with the enrollment records; any missed patients will be noted in our tracking records and, if necessary, the project manager will follow-up with study personnel. To ensure consent and data collection procedures are properly followed and potential issues are promptly addressed, the PI and project manager will conduct monthly teleconference calls with all study personnel. They will discuss current enrollment and potential concerns regarding enrollment, consent documents, or data collection procedures and tools. Further, the project manager will touch base one-on-one with all study personnel at least once every month to address any specific issues.

Lastly, we will review all data collection packets, including consent documents and health information releases, to ensure proper completion. All data collection records in REDCap will be reviewed by the project manager to check for accuracy and completion. Revisions to the data collection forms will be completed as necessary.

### 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 recovery coaches and research assistants at the site under the supervision of the project manager and principal investigator. The recovery coaches and research assistants will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported, and the project manager will review each 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. 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.

#### 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 NIDA and 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. Due to agreements with the agencies providing de-identified data for this study, we are unable to make the dataset public. However, we will share a limited dataset with interested parties who are willing to sign a specific data-sharing agreement. The limited dataset will not include any information from the INSPECT prescription drug monitoring database due to concerns of the board members overseeing it. The data-sharing agreement will stipulate the interested party must: (1) commit to using the data for research purposes only; (2) secure the data using appropriate precautions and technology; (3) commit to returning or destroying the data after analyses are completed.

### 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. The study leadership in conjunction with the NIDA has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

## 10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

## 10.3 ABBREVIATIONS AND SPECIAL TERMS

| | |
|---|---|
| ACEs | Adverse Childhood Experiences |
| AE | Adverse Event |
| CFR | Code of Federal Regulations |
| CITI | Collaborative Institutional Training Initiative |
| COC | Certificate of Confidentiality |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| DSMB | Data Safety Monitoring Board |
| ED | Emergency Department |
| EMS | Emergency Medical Services |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICH | International Council on Harmonisation |
| INSPECT | Indiana Scheduled Prescription Electronic Collection & Tracking Program |
| IRB | Institutional Review Board |
| IU | Indiana University |
| IV | Intravenous |
| MOUD | Medication for Opioid Use Disorder |
| NIH | National Institutes of Health |

| | |
|---|---|
| NIDA | National Institute on Drug Abuse |
| OHRP | Office for Human Research Protections |
| OUD | Opioid Use Disorder |
| PI | Principal Investigator |
| POINT | Planned Outreach, Intervention, Naloxone, and Treatment |
| RA | Research Assistant |
| RC | Recovery Coach |
| REDCap | Research Electronic Data Capture |
| SAE | Serious Adverse Event |
| SOA | Schedule of Activities |
| US | United States |

## 10.4 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

| Version | Date | Description of Change | Brief Rationale |
|---|---|---|---|
| 2 | 2/14/18 | Amended the eligibility criteria to include the time of discharge (rather than the time of admission).<br><br>Amended the interview criteria so that interviews can be conducted in any private area (rather than be restricted to the patient's ED area). | We learned that patients can stay in the ED for long durations that might extend beyond an enrollment shift. Thus, a research staff person or recovery coach might have completed their shift by the time the patient is ready to be enrolled. The discharge time aligned more closely with the time of enrollment.<br><br>Due to limited space, patients might need to complete interviews in another private area to make room for new hospital patients. |
| 3 | 3/30/18 | Expanded the eligibility criteria from only opioid overdoses to opioid-related issue (including withdrawal, abscess, intoxication).<br><br>Amended the enrollment shifts to 24 hours, rather than excluding 12am-7:59am. | Hospital staff informed us that a large volume of patients with opioid addiction enter the ED for non-overdose related issues.<br><br>Hospital staff informed us that patients can be discharged from the ED overnight and admitted to inpatient care (i.e., still able to be enrolled onsite by staff). |
| 4 | 4/18/18 | Amended eligibility criteria so that patients may be eligible if deemed "cleared for discharge by a provider" (rather than "discharged from the ED").<br><br>Expanded the eligibility criteria to include endocarditis. | We learned that patients often want to exit the ED as soon as they are officially discharged and do not want to spend extra time enrolling in a study. Changing the timing allowed us to utilize the time in between clearance and official discharge, while administrative tasks are completed. |

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|---|---|---|---|
| | | | Hospital staff informed us that a high volume of patients enter the ED for endocarditis, related to opioid addiction. |
| 5 | 10/16/18 | Added IU Health Ball Memorial as a study site. | Initial enrollment occurred at IU Health Methodist and then expanded to IU Health Ball Memorial. |
| 6 | 4/11/19 | Amended the recruitment and eligibility process to include the DSM-5 for Opioid Use Disorder as a screening tool for eligibility. Participants must score at least "1" on this screening tool to be eligible.<br><br>Amended the REDCap questionnaire to include the 16-item Subjective Opioid Withdrawal Scale (SOWS). | We identified that some individuals were coming through the ED whose overdose was the result of occasional recreational use of opioids or adulteration of another drug with fentanyl; therefore, these individuals would not have an opioid use disorder and be inappropriate for MOUD treatment linkage. |
| 7 | 2/6/20 | Amended protocols so that RAs & RCs may enter the room and introduce the study prior to their discharge clearance. They must still wait for discharge clearance before consenting/collecting data. | We identified that this would have less of an impact on the ED workflow and result in less delays to patient discharge as a result of data collection. |