ClinicalTrials.gov ID: NCT05370326

Title: Feasibility and Preliminary Efficacy of an Opioid Stewardship Program in Hospitalized Patients With Chronic Pain

Document: Protocol with SAP

Date: 5/4/2022

CLINICAL STUDY PROTOCOL

Observational Study of Individual or Group Template

Randomized Controlled Pilot Trial to Evaluate Feasibility and Preliminary Efficacy of an Opioid Stewardship Program in Hospitalized Patients with Chronic Pain

Protocol Number

Yale HIC#2000032638

Protocol Version

April 2022

1

Confidentiality Statement:

Synopsis

Purpose The purpose of this work is to investigate the feasibility and preliminary efficacy of an enhanced opioid stewardship program, tailored to the needs of hospitalized patients with chronic pain with opioid dependence, incorporating real-time guidance from an addiction medicine and pain-trained physician/pharmacist team, using a pilot randomized clinical trial format. Findings from this research may improve pain management and decrease risk of opioid-related adverse events among patients with chronic pain.
Primary Objective The primary objective of this study is to determine whether an enhanced opioid stewardship program, tailored to the needs of patients with chronic pain, is feasible to implement in a hospital setting.
Secondary Objective One secondary objective is to determine whether an enhanced opioid stewardship program increases use of guideline-based opioid care. The other secondary objective of this study is to determine whether an enhanced opioid stewardship program reduces pain frequency, intensity, and interference and decreases the risk for opioid-related adverse events among adult patients with chronic pain hospitalized on medical units at Yale-New Haven Hospital, York Street and Saint Raphael campuses.
Study Design We propose a pilot randomized controlled trial of 100 adult patients hospitalized on medicine units at Yale-New Haven Hospital York Street Campus and Saint Raphael campus. The trial will be prospective and focus primarily on feasibility.
Study Date Range and Duration The study will commence upon IRB approval. The duration of participation for each study subject will include days in the hospital from study enrollment to discharge and 30 days after discharge. Therefore, the minimum duration of the study is 30 days.
Number of Study Sites The study will take place at one site: Yale New Haven Hospital (YSC and SRC).
Primary Outcome Variables The primary outcomes for this pilot RCT will relate to feasibility of recruitment and retention. For recruitment, we will describe the number of patients screened vs. the number of patients eligible; the number of patients eligible vs. the number enrolled; and the hospital day of enrollment (in relation to the admission and discharge dates). For retention, we will describe the number of participants in the intervention group for whom

we are able to deliver the full enhanced opioid stewardship intervention, as well as the number in intervention and control groups who complete the peri-discharge evaluation.

Secondary and Exploratory Outcome Variables (if applicable)

A secondary outcome for this pilot RCT will include a count of guideline-based care elements considered to be “best practices” for opioid stewardship in the setting of chronic pain. These include ordering of alternative pain relief medications (e.g., acetaminophen), ordering of a bowel regimen, ordering of medication to treat opioid use disorder, order of urine toxicology screen, ordering of ECG for patients prescribed methadone, avoidance of co-prescriptions of benzodiazepines, and other associate “best care” practices. These metrics will be abstracted from the medical record.

Other secondary outcomes will include pain frequency, intensity, and interference, assessed using a modified Brief Pain Inventory.[1] Depression and anxiety will be measured using the Patient Health Questionnaire-4.[2] Participant satisfaction with pain care will also be assessed at discharge. ED visits and readmissions at the 30 days post-discharge from the hospitalization in which the participant is recruited will also be abstracted from the medical record.

Study Population

The study population will be comprised of adult patients (>=18 years) hospitalized on medical units at YNHH YSC and SRC with chronic pain and opioid use. Eligible patients can be hospitalized for any medical condition (i.e., admission diagnoses do not need to be related to chronic pain). Patients will be identified by a pre-specified case identification tool (i.e., Epic report).

Number of Participants

We will enroll 100 participants for this feasibility study.

Study Schedule

The total number of visits as part of this intervention will include (1) screening and consent, (2) baseline interview (may be combined with consent visit, per participant’s preference), and (3) a peri-discharge interview (within 48 hours of anticipated discharge). The total number of study visits is expected to be three per participant, with the potential for greater frequency of interaction via phone. Each visit will last approximately 30 minutes or less.

Protocol Revision History

Version Date	Summary of Substantial Changes

Statement of Compliance

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to the Common Rule at 45CFR46 (human subjects) and other applicable government regulations and Institutional research policies and procedures.

Abbreviations

Abbreviation	Explanation

CP: chronic pain

MOUD: medications to treat opioid use disorder

OUD: opioid use disorder

Table of Contents

1 Background/Literature Review

1.1 Background

Many patients with CP who receive long term opioid therapy will experience opioid dependence and are at risk for opioid-related harms, including opioid use disorder (OUD),. Hospitalizations of patients with CP and opioid dependence are increasing nationally[3] and are an important opportunity to optimize the use of medications for CP and OUD, when indicated. Hospitalizations can also be risky for this patient population, as opioids are the second most common cause of preventable adverse events in hospitalized patients.[4] Administration of opioids and other controlled substances such as benzodiazepines contribute to new episodes of or higher dosages of long-term opioids after hospital discharge. Notably, there has been increased recognition of the "stress of hospitalization," including sleep deprivation, immobility, and uncertainty about care plans.[5] This stress may exacerbate CP, anxiety and depression. Our work has demonstrated that generalist prescribers rarely follow opioid prescribing guidelines[6-8] and most prescribing decisions regarding CP and opioid dependence during hospitalization are made by clinicians with limiting training in the management of these conditions. As a result, front-line hospital prescribers often do not prescribe opioids and other controlled substances according to best practices for patients with CP and opioid dependence, with or without OUD. While addiction consult services are growing, they are not always involved in the care of patients with CP and are limited to a small number of academic medical centers.

Recently "opioid stewardship" programs, modelled after "antibiotic stewardship" programs that manage the adverse individual and public health effects of antibiotic prescribing that does not adhere to guidelines, have been created by hospitals to improve opioid prescribing in the hospital setting.[4,9] These programs, endorsed by the Joint Commission (the entity that accredits hospitals nationally), bring focused expertise to promote the appropriate use of opioids and improve patient outcomes. They are consistent with the Joint Commission's mandate in 2018 for hospitals to implement leadership teams and performance improvement processes to address opioid prescribing. However, a 2020 survey of hospitals reported that only 14% prospectively identified patients in need of stewardship services – the model we propose.[4] Prospective opioid stewardship programs vary by hospital but typically use automated case finding to identify eligible patients and then implement medication and non-medication treatments balancing opioid risks, often assessed as milligram morphine equivalents (MMEs), and benefits, often assessed using measures of pain and pain interference.

While there is growing use of hospital-based opioid stewardship programs, they have not been tailored to the needs of patients with CP and opioid dependence, with or without OUD. Hospitalized patients with CP and opioid dependence, and the clinicians who care for them, face a range of key decisions regarding each condition. For instance, the management of methadone, buprenorphine and naltrexone for patients with OUD involves clinical considerations including important patient preferences. Additionally, hospitalized patients with CP and opioid dependence can experience both acute pain from injury, surgery or medical procedures as well as exacerbations of CP during hospitalization that require tailored treatment. Clinical decisions about which medication and non-medication-based pain treatments to deploy involve weighing risks and benefits, including the impact of treatments on OUD and comorbid anxiety and depression. These decisions, especially those related to medications, may have important consequences with respect to CP, opioid dependence with or without OUD, anxiety, depression and health care utilization. There are few published studies to inform stakeholders regarding the efficacy of hospital-based opioid stewardship, especially in patients with CP and opioid dependence.

The Yale-New Haven Hospital System has implemented an opioid stewardship program, modelled after "antibiotic stewardship" programs that manage the adverse

individual and public health effects of antibiotic prescribing, to improve opioid prescribing in the hospital setting.[4] This program, endorsed by the Joint Commission, brings focused expertise to promote the appropriate use of opioids and improve patient outcomes through opioid use monitoring and development of "best practice" recommendations regarding opioid prescribing. However, the YNHHS Opioid Stewardship Program has limited impact on the care of individual patients, as the only patient-specific intervention implemented is the delivery of automated "best practice alerts" (i.e., "pop-ups") through the electronic medical record of clinicians.

The purpose of the proposed study is to evaluate the feasibility and preliminary efficacy of an opioid stewardship program that provides real-time interaction and guidance from an addiction medicine and pain-trained physician/pharmacist team, focusing on implementing and tailoring best practices for use of opioids for patients hospitalized with CP and opioid dependence. We propose to evaluate the implementation and assess preliminary efficacy of the intervention.

1.2 Prior Experience (if applicable)

Drs. Weimer, Fiellin, and Becker have extensive experience using electronic medical record data to identify patients with chronic pain.[8,10-20] Drs. Chaudhry and Hajduk have experience conducting hospital-based intervention studies including those focused on transitions of care.[21-29] YNHH currently has an opioid stewardship program, chaired by Dr. Ackerman with Dr. Weimer as a member, that employs system-based opioid surveillance such as a dashboard to identify patients receiving opioids, automatic "best practice" prompts in the electronic medical record to avoid opioid prescribing when opioids have not been used in the previous 24 hours, and automatic "best practice" prompts to prescribe naloxone at discharge for patients who are prescribed opioids greater than a certain dose. The study proposed will leverage existing YNHH clinical pharmacy staff and opioid stewardship resources. Dr. Weimer has also developed landmark hospital-based Addiction Medicine Consult Programs and developed nationally recognized pain and OUD treatment education for clinicians.[30-34] Dr. Ackerman has led innovations to address hospital opioid prescribing.[35] **Relevance:** The investigators have experience using electronic medical records to identify patients with chronic pain and OUD and in conducting hospital-based intervention studies. The proposed work will evaluate the feasibility and efficacy of an enhanced version of an existing opioid stewardship program to meet the needs of hospitalized patients with chronic pain and opioid misuse. Rationale/Significance

1.3 Rationale and Study Significance

Hospitalizations of patients with CP and opioid dependence are increasing nationally[3] and are an important opportunity to optimize the use of medications for CP and OUD, when indicated. Hospitalizations can also be risky for this patient population, as opioids are the second most common cause of preventable adverse events in hospitalized patients.[4] For example, administration of opioids and other controlled substances such as benzodiazepines can contribute to new episodes of or higher dosages of long-term opioids after hospital discharge. Additionally, there has been increased recognition of the "stress of hospitalization," including sleep deprivation, immobility, and uncertainty about care plans.[5] This stress may exacerbate CP, anxiety and depression. Our work has demonstrated that generalist prescribers rarely follow opioid prescribing guidelines[6-8] and most prescribing decisions regarding CP and opioid dependence during hospitalization are made by clinicians with limiting training in the management of these conditions. As a result, front-line hospital prescribers often do not prescribe opioids and other controlled substances according to best practices for patients with CP and opioid dependence, with or without OUD. While addiction consult services are growing, they are not always involved in the care of patients with CP, and are limited to a small number of academic medical centers.

There are a range of key decisions regarding hospitalized patients with CP and opioid dependence that clinicians face. For instance, the management of methadone, buprenorphine and naltrexone for patients with OUD involves clinical considerations including important patient preferences. Additionally, tailored treatment may be necessary for hospitalized patients with CP and opioid dependence who experience both acute pain from injury, surgery or medical procedures as well as exacerbations of CP during hospitalization. Clinical decisions about which medication and non-medication-based pain treatments to deploy involve weighing risks and benefits, including the impact of treatments on OUD and comorbid anxiety and depression. These decisions, especially those related to medications, may have important consequences with respect to CP, as well as opioid dependence with or without OUD, anxiety, depression and health care utilization.

Interventions that maximize benefits and minimize risks of opioid prescribing for hospitalized patients with CP and opioid dependence are critically needed as this becomes an increasingly common clinical scenario. Currently, the YNHHS Opioid Stewardship Program, modelled after “antibiotic stewardship” programs that manage the adverse individual and public health effects of antibiotic prescribing, aims to improve opioid prescribing in the hospital setting however has limited impact on the care of individual patients as the only patient-specific intervention implemented is the delivery of automated “best practice alerts” (i.e., “pop-ups”) through the electronic medical record. The proposed study intervention will build on to current Opioid Stewardship Program by including real-time interaction and guidance from an addiction medicine and pain-trained physician/pharmacist team, focusing on implementing and tailoring best practices for use of opioids for patients hospitalized with CP and opioid dependence.

1.4 Purpose of Study/Potential Impact

The purpose of this work is to investigate the feasibility and preliminary efficacy of an enhanced opioid stewardship program, tailored to the needs of hospitalized patients with chronic pain with opioid dependence, incorporating real-time guidance from an addiction medicine and pain-trained physician/pharmacist team, using a pilot randomized clinical trial format. Findings from this research may improve pain management and decrease risk of opioid-related adverse events among patients with chronic pain.

1.5 Potential Risks and Benefits

1.5.1 Potential Risks

Opioid Stewardship Intervention: The goal of the enhanced opioid stewardship intervention is to manage chronic pain while reducing risk of inappropriate/risky opioid use and preventing harms of opioid use. We anticipate no significant adverse effects from participating in the opioid stewardship intervention. It is important to note that the intervention team will not have a direct impact on patient care; all guidance related to appropriate pain management and adjuvant therapies will be provided to a participant’s clinical team, who will be ultimately responsible to decide whether to apply such guidance to their patient’s care. Nonetheless, there is a small chance that efforts to manage pain in the context of best practices for opioid use may inadvertently and temporarily result in distress in

participants. Distress may include temporary increases in pain or physical or mental discomfort from opioid withdrawal symptoms. All patients will receive best practice treatment for their withdrawal symptoms and treatment of OUD, if present, as part of usual clinical care.

Rating scales and questionnaires: Rating scales and questionnaires are all non-invasive, however, some questions may be distressing to participants.

Confidentiality: There is a small risk of a breach of data or private information associated with participation in this study.

1.5.2 Potential Benefits

Participants in this pilot RCT may potentially derive certain benefits, although none are guaranteed. Immediate potential benefits include improved pain management, including decreased severity or frequency of pain, and reduced interference from pain in going about daily activities. Another immediate potential benefit would be reduced risk of opioid-related adverse events during hospitalization, including over-sedation, gastrointestinal side effects, as well as identification of an opioid use disorder, leading to treatment consistent with usual care (which would be recommended by the intervention team). Potential long-term benefits include decreased risk of developing OUD or improved treatment of an existing OUD, and better pain management and quality of life. These benefits would apply primarily to the intervention group. The control group will be treated with usual hospital-based care.

2 Study Purpose and Objectives

2.1 Hypothesis

Participants randomized to the intervention will have less pain, fewer opioid-related adverse events, and greater improvement in quality of life compared with control participants, as measured at hospital discharge.

The care of intervention participants will also include a greater number of guideline-based care elements for opioid stewardship compared with the care of control participants, as measured at hospital discharge.

2.2 Primary Objective

The primary objective of this study is to determine whether an enhanced opioid stewardship program, tailored to the needs of patients with chronic pain, is feasible to implement in a hospital setting. Feasibility will be measured using standard metrics and are described in Section 3.2.1.

2.3 Secondary Objective (if applicable)

There are two secondary objectives to this pilot RCT, both related to efficacy.
One secondary objective is to determine whether an enhanced opioid stewardship program increases use of guideline-based opioid care. The other secondary objective of this study is to determine whether an enhanced opioid stewardship program reduces pain frequency, intensity, and interference and decreases the risk for opioid-related adverse events among

adult patients with chronic pain hospitalized on medical units at Yale-New Haven Hospital, York Street and Saint Raphael campuses. Outcomes for the secondary objectives are described in section 3.2.2.

3 Study Design

3.1.1 General Design Description

We propose a pilot randomized controlled trial of 100 adult patients hospitalized on medicine units at Yale-New Haven Hospital York Street Campus and Saint Raphael campus. The trial will be prospective and focus primarily on feasibility.

3.1.2 Study Date Range and Duration

The study will commence upon approval of this IRB application (expected April 2022) and will finish upon completion of all study activities for 100 enrolled participants. The expected duration of participation by a given participant will be from the day of enrollment to 30 days after discharge from the admission during which they were enrolled.

.

3.1.3 Number of Study Sites

There will be one study site- Yale-New Haven Hospital, SRC and YSC campuses.

3.2 Outcome Variables

3.2.1 Primary Outcome Variables

The primary outcomes for this pilot RCT will relate to feasibility of recruitment and retention. For recruitment, we will describe the number of patients screened vs. the number of patients eligible; the number of patients eligible vs. the number enrolled; and the hospital day of enrollment (in relation to the admission and discharge dates). For retention, we will describe the number of participants in the intervention group for whom we are able to deliver the full enhanced opioid stewardship intervention, as well as the number in intervention and control groups who complete the peri-discharge evaluation.

3.2.2 Secondary and Exploratory Outcome Variables (if applicable)

A secondary outcome for this pilot RCT will include a count of guideline-based care elements considered to be “best practices” for opioid stewardship in the setting of chronic pain. These include ordering of alternative pain relief medications (e.g., acetaminophen), ordering of a bowel regimen, ordering of medication to treat opioid use disorder, order of urine toxicology screen, ordering of ECG for patients prescribed methadone, avoidance of co-prescriptions of benzodiazepines, and other associate “best care” practices. These metrics will be abstracted from the medical record.

Other secondary outcomes will include pain frequency, intensity, and interference, assessed using a modified Brief Pain Inventory.[1] Depression and anxiety will be measured using the Patient Health Questionnaire-4.[2] Participant satisfaction with pain care will also be assessed

at discharge. ED visits and readmissions at the 30 days post-discharge from the hospitalization in which the participant is recruited will also be abstracted from the medical record.

3.3 Study Population

The study population will be comprised of adult patients (>=18 years) hospitalized on medical units at YNHH YSC and SRC with chronic pain and opioid use. Eligible patients can be hospitalized for any medical condition (i.e., admission diagnoses do not need to be related to chronic pain). Patients will be identified by a pre-specified case identification tool (i.e., Epic report).

3.3.1 Number of Participants

We anticipate 10-50 records will be returned in the Epic report each day that will be screened for eligibility. We aim to recruit 100 participants who meet all inclusion and exclusion criteria for the trial, for a total of approximately 50 each in the intervention and control arms. Screening and enrollment will continue until the target sample size has been reached, with a goal of recruiting 5-10 patients per week.

Eligibility Criteria/Vulnerable Populations

In order to be eligible for inclusion in the study, an individual must meet all of the following criteria:

- adults (age ≥18 years);
- admitted at YNHH (YSC and SRC) on medical units;
- identified as having chronic pain and prescribed opioids.
- Have opioid dependence (evidenced by ongoing opioid prescription, meeting DSM-5 criteria for OUD, or clinical history)

Any individual who meets any of the following criteria will be excluded from participation in this study:

- active cancer
- current pregnancy
- hospice care/comfort measures only
- admission to inpatient psychiatry
- completed or planned Addiction Medicine consult during hospitalization

4. Study Methods/Procedures

3.4 Study Procedures

All patients will receive standard hospital care. Patients who are identified as eligible for the study via screening in Epic will be approached during hospitalization, undergo informed consent, and be enrolled in the study. Those who consent will be asked questionnaires

related to patient reported outcomes of pain, anxiety, depression and quality of life at baseline. Patients will then be randomized on a 1:1 ratio to either the enhanced opioid stewardship program arm or a control (i.e., usual care) arm. Patients who are randomized to the intervention arm will have their medical record reviewed by both a pharmacist and a physician trained in pain and addiction medicine. The pharmacist and physician will provide best practice guidance via an Epic note to the primary care teams to consider, versus continuation with their usual care plan. All guidance will be voluntary for clinical teams to follow. All participants will be tracked daily in Epic for discharge status, and when discharge within 48 hours is anticipated, the study team will perform the final patient interview, which will be very similar to the baseline interview and composed of questionnaires related to pain, anxiety, depression, and quality of life. Medical record abstraction will be performed to abstract relevant characteristics of each participant's hospitalization, use of guideline-based best practices for pain management and opioid stewardship at discharge, and incidence of readmissions and ED visits within 30 days after discharge for the hospitalization during which the participant was recruited.

3.4.1 Data Collection

All data collection will occur via password-protected and HIPAA compliant data entry and management software, Research Electronic Data Capture (REDCap). Potential participants will be given unique study IDs at the outset of recruitment that will be used throughout the study to minimize use of identifiers. Only authorized study personnel will have access to files that link study IDs to identifiable data.

3.4.2 Adverse Events Definition and Reporting

Because the trial will not directly intervene on the clinical care of participants but will rather offer suggestions for care of participants with regard to pain management and opioid stewardship to a given participant's medical team, we anticipate that the risk for adverse events that are attributable to participation in the clinical trial will be minimal. We will monitor all participants during their participation in the trial for (1) death, (2) development of an adverse reaction to a recommended intervention (e.g., new medication) requiring medical care, and (3) increases in pain assessed via the numeric rating scale (standard hospital practice) requiring a change in medical care. We will notify the Yale HIC of these adverse events, and any other anticipated adverse events, immediately upon notification of the PI and will provide written documentation within 5 days.

3.5 Study Schedule

The total number of visits as part of this intervention will include (1) screening and consent, (2) baseline interview (may be combined with consent visit, per participant's preference), and (3) a peri-discharge interview (within 48 hours of anticipated discharge). The total number of study visits is expected to be three per participant, with the potential for greater frequency of interaction via phone. Each visit will last approximately 30 minutes or less.

Study Schedule:

Study Activity	Time frame/duration
1. Currently hospitalized patients screened in Epic	Every weekday
2. Eligible participants approached by study team	Every weekday
3. Study described, questions answered, written informed consent obtained	30 minutes
4. Participant completes baseline interview; $25 gift card provided	15 minutes
5. Participant randomized to intervention or usual care arm	1 minute
6. Participant's hospitalization tracked for anticipated discharge status	Daily
7. Intervention participants' charts reviewed by study team's addiction medicine physician/pharmacist for adherence to best practice guidelines for pain management/opioid stewardship.	Once, within 24 hours of randomization
8. Study addiction medicine physician composes note in intervention participant's medical record with recommendations to optimize guideline-based pain management/opioid stewardship	Once
9. Study addiction medicine physician alerts primary clinical care team via Mobile Heart Beat of Epic note regarding guideline-based care recommendations	Once
10. Final participant interview performed within 48 hours of anticipated discharge; $25 gift card provided	15 minutes
11. Medical record abstraction performed for hospitalization characteristics, use of guideline-based best practices for pain management/opioid stewardship, and readmissions/ED visits within 30 days	1-30 days post-discharge

3.6 Informed Consent

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. Potential participants will be offered the following consent materials are submitted with this protocol: consent form.

3.6.1 Screening (if applicable)

The PI and RA will be responsible for performing all screening activities. After receiving training from the investigative team faculty, the RA will screen each weekday a dedicated Epic report that identifies adult inpatients hospitalized on medicine units at Yale-New Haven Hospital YSC and SRC who are on the YNHH Opioid Registry and have not opted out of research in the YNHHS. Charts of each patient on the Epic report will be reviewed to confirm absence of exclusion criteria. The RA will consult the PI with any questions regarding eligibility. Data on the number of patients screened and number of eligible patients will be recorded in daily screening logs in REDCap for recruitment tracking purposes.

3.6.2 Recruitment, Enrollment and Retention (if applicable)

Eligible patients will be approached by the RA during hospitalization. The RA will first check in with the clinical team (e.g., charge nurse) to confirm appropriateness and timing of approach.

The RA will provide an overall description of the study and gauge the patient's interest. If the patient is potentially interested in participating, the RA will begin the informed consent process- this will include providing details about the structure and format of study participation, the disclosure of potential benefits and risks, and confirmation that study participation is completely voluntary and will not in any way affect the care the patient receives at YNHSS or elsewhere. The patient will be provided with a paper consent form to review with the RA and will be given ample time to review independently or with family members. The patient will then be provided an opportunity to ask questions about the study. Once the RA has answered all questions, the participant will be asked to sign the informed consent form, indicating their understanding and willingness to participate in the study. The consent form will be scanned into REDCap for record keeping. A copy of the form will be given to the participant to keep. Study participation will commence after the signing of the informed consent form and will last until 30 days after discharge from the hospitalization during which the participant was enrolled in the study.

3.6.3 Study Visits (if applicable)

There will be up to 3 study visits with each participant, which will take place during hospitalization or in the first week after hospital discharge.

The first study visit will be for recruitment and enrollment. This visit will follow the format described in Section 3.6.2. This visit will last approximately 30 minutes.

The second study visit will be for completion of the baseline interview. This study visit may occur directly after enrollment. During this interview, participants will be asked questions related to pain, depression, and anxiety. Pain will be assessed using an abridged version of the Brief Pain Inventory,[1] which will take 5 minutes to complete. Depression and anxiety will be assessed with the Patient Health Questionnaire-4,[2] which will take 2 minutes to complete. They will also be asked demographic questions, for descriptive purposes. The baseline interview visit will last approximately 15 minutes.

The third study visit will be for completion of the final interview, which will take place within 48 hours of anticipated discharge. Participants will answer questions identical to those asked in the baseline interview on pain, depression, and anxiety. They will also be asked one question regarding their satisfaction with pain: "How pleased are you with your pain outcome during this hospital visit?," which will be answered on a Likert-type scale. The final interview will last approximately 15 minutes.

3.7 Statistical Method

3.7.1 Statistical Design

The design of this this study is a randomized controlled trial. Due to the pilot nature of this trial, statistical considerations will consist primarily of bivariate analyses (i.e., t-tests, rank sum, and chi-square tests, as appropriate to variable type) to ensure balance of covariates

between randomization groups and also to explore unadjusted associations between randomization groups and our outcomes. Exploratory regression analyses may be utilized to evaluate multivariable-adjusted associations between randomization groups and our outcomes, particularly if an imbalance between covariates among randomization groups is discovered.

3.7.2 Sample Size Considerations

This pilot trial was not developed with power in mind to find a particular effect size in outcomes between study arms; hence we do not include power calculations.

3.7.3 Planned Analyses

Due to the pilot nature of this trial, statistical considerations will consist primarily of bivariate analyses (i.e., t-tests, rank sum, and chi-square tests, as appropriate to variable type) to ensure balance of covariates between randomization groups and also to explore unadjusted associations between randomization groups and our outcomes. Exploratory regression analyses may be utilized to evaluate multivariable-adjusted associations between randomization groups and our outcomes, particularly if an imbalance between covariates among randomization groups is discovered.

3.7.4 Analysis of Subject Characteristics (if applicable)

Subject characteristics will be evaluated using standard descriptive statistics and bivariate analyses **(i.e., t-tests, rank sum, and chi-square test)** to evaluate differences between intervention and control arms.

3.7.5 Interim Analysis (if applicable)

n/a

3.7.6 Handling of Missing Data

Approaches to manage missing data will not be implemented in this pilot study- missing data will indeed be part of our feasibility outcomes.

5 Trial Administration

4.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The Research Associate will explain the research study to the participant and answer any questions that may arise. This conversation will take place in a private room. The Research Associate will also provide the name and contact information of the PI, who the prospective participant can contact directly with questions.

Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates, or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants will 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 participant for their records

4.2 Institutional Review Board (IRB) Review

The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol or study team will require an approved IRB amendment before implementation. The IRB will determine whether informed consent and HIPAA authorization are required.

A study closure report will be submitted to the IRB after all research activities have been completed.

4.3 Subject Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

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

The study monitor, representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored on password-protected server internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or, if applicable, sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in REDCap. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study ID. The study data entry and study management systems used will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Yale REDCap archiving system.

4.4 Deviations/Unanticipated Problems

The PI will report any protocol deviations, whether on the part of the participant, investigator(s), or study staff, to the Yale IRB within 5 days of becoming aware of the deviation. Deviations will be tracked in study source documents (i.e., a central tracking sheet) and reported to the study sponsor.

The PI will report unanticipated problems (UPs), defined as problems that are unexpected in terms of nature, severity, or frequency given the research procedures described in the study protocol and associated documents and result in a greater risk of harm than was previously recognized, to the Yale IRB and to the study sponsor. The PI will work with the Yale IRB and/or sponsor to determine whether the UP is related or possibly related to participation in the trial. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and study sponsor, if applicable within five days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and study sponsor within five daysof the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within five days of the IRB's receipt of the report of the problem from the investigator.

The protocol and consent forms will be updated to reflect new knowledge of potential risks within 30 days. Inclusion and exclusion criteria, as well as information regarding management of any newly discovered study-related risks, will be included in protocol and consent form modifications, and will be submitted to the Yale IRB in a timely manner.

4.5 Data Quality Assurance

Data quality will be monitored via automated quality checks in REDCap and frequent review of data by the investigative team. All members of the investigative team will be trained in accurate data collection and reporting processes prior to the start of data collection. Automated elements to be integrated into REDCap data collection forms include “response required” settings for critical data, out-of-range alerts for quantitative data, and “completion status” confirmation questions for all data collection forms. All data entry and modification will be tracked using automated audit trails. Data will be reviewed on a weekly basis by the investigative team for completeness and identification of possible out-of-range/extreme values.

4.6 Study Records

Documents to be considered study records include: screening forms; enrollment forms; signed informed consent forms; baseline interview; final interview; guideline-based care notes from addiction medicine physician/pharmacist team; and post-discharge and 30-day medical record abstraction forms.

4.7 Access to Source

Source data will be maintained per Medical Records policy in a password protected, secure, Health Insurance Portability and Accountability Act (HIPAA) compliant, web-based electronic database with a built-in audit trail, i.e., REDCap
Only Institutional Review Board (IRB) approved research team members who have current HIPAA and Collaborative Institutional Training Initiative (CITI) Good Clinical Practice (GCP) and human subjects protection training will be authorized to access records.

4.8 Data or Specimen Storage/Security

All data will be collected and stored digitally in REDCap. REDCap is secure, password-protected, and HIPAA-compliant.

4.9 Retention of Records

Study records will be retained for a minimum of three years after completion of the study and submission of the final progress report, in accordance with NIH policy. At that time, all data, including the master list linking the unique study ID to identifiers, will be destroyed.

4.10 Study Monitoring

Because this is a small pilot RCT with a focus on feasibility outcomes, there will be no external DSMB. Study progress and data will be reviewed weekly by the investigative team for accuracy, led by the PI.

4.11 Study Modification

All study modifications will be submitted for review and approval by the Yale HIC. Study modifications will not be implemented until the Yale HIC has approved the modification.

4.12 Study Completion

The anticipated completion date of the study is November 2023. The study team will notify the Yale HIC of study completion via a request to close the study record in IRES.

4.13 Funding Source

The study is funded as a pilot project of NIH/NIDA RM1 DA055310, the “HEAL Initiative: Integrative Management of Chronic Pain and OUD for Whole Recovery (IMPOWR): Research Centers.”

4.14 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 trial. The study leadership, in conjunction with the appropriate conflict of interest review committee, 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.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the

conflict reviewed by the [specify committee] with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All investigators will follow the applicable conflict of interest policies.

4.15 Publication Plan

We plan to present study findings at national conferences and include as preliminary data in future grants. We will also aim to produce one manuscript for publication that details the associations between the intervention and our feasibility and preliminary efficacy outcomes.

Appendices

Appendix #	Title	Section	Topic

1. Brief Pain Inventory (validated survey instrument, uploaded in IRES)

2. Patient Health Questionnaire-4 (validated survey instrument, uploaded in IRES)

References

1. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap.* 1994;23(2):129-138.
2. Kroenke K, Spitzer RL, Williams JB, Lowe B. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. *Gen Hosp Psychiatry.* 2010;32(4):345-359.
3. Weiss AJ, Elixhauser A, Barrett ML, Steiner CA, Bailey MK, O'Malley L. Opioid-Related Inpatient Stays and Emergency Department Visits by State, 2009-2014: Statistical Brief #219. *Healthcare Cost and Utilization Project (HCUP) Statistical Briefs*. Rockville (MD)2006.
4. Ardeljan LD, Waldfogel JM, Bicket MC, et al. Current state of opioid stewardship. *Am J Health-Syst Ph.* 2020;77(8):636-643.
5. Krumholz HM. Post-hospital syndrome--an acquired, transient condition of generalized risk. *N Engl J Med.* 2013;368(2):100-102.
6. Gaither JR, Goulet JL, Becker WC, et al. The Effect of Substance Use Disorders on the Association Between Guideline-concordant Long-term Opioid Therapy and All-cause Mortality. *Journal of addiction medicine.* 2016;10(6):418-428.
7. Gaither JR, Goulet JL, Becker WC, et al. The Association Between Receipt of Guideline-Concordant Long-Term Opioid Therapy and All-Cause Mortality. *J Gen Intern Med.* 2016;31(5):492-501.
8. Gaither JR, Goulet JL, Becker WC, et al. Guideline-concordant management of opioid therapy among human immunodeficiency virus (HIV)-infected and uninfected veterans. *J Pain.* 2014;15(11):1130-1140.
9. Vien A, Shyh G, Jannat-Khah D, et al. Impact of a Novel Hospital-Based Opioid Stewardship Program on Nonsurgical Acute Pain Management in the Hospital. *J Gen Intern Med.* 2021.
10. Wyse JJ, Robbins JL, McGinnis KA, et al. Predictors of timely opioid agonist treatment initiation among veterans with and without HIV. *Drug and alcohol dependence.* 2019;198:70-75.
11. Barry DT, Goulet JL, Kerns RK, et al. Nonmedical use of prescription opioids and pain in veterans with and without HIV. *Pain.* 2011;152(5):1133-1138.
12. Becker WC, Fiellin DA, Gallagher RM, Barth KS, Ross JT, Oslin DW. The association between chronic pain and prescription drug abuse in Veterans. *Pain Medicine.* 2009;10(3):531-536.
13. Becker WC, Gordon K, Jennifer Edelman E, et al. Trends in Any and High-Dose Opioid Analgesic Receipt Among Aging Patients With and Without HIV. *AIDS and behavior.* 2015.
14. Edelman EJ, Gordon K, Becker WC, et al. Receipt of opioid analgesics by HIV-infected and uninfected patients. *J Gen Intern Med.* 2013;28(1):82-90.
15. Weisberg DF, Gordon KS, Barry DT, et al. Long-term Prescription of Opioids and/or Benzodiazepines and Mortality Among HIV-Infected and Uninfected Patients. *Journal of acquired immune deficiency syndromes (1999).* 2015;69(2):223-233.
16. Lovejoy TI, Dobscha SK, Turk DC, Weimer MB, Morasco BJ. Correlates of prescription opioid therapy in Veterans with chronic pain and history of substance use disorder. *Journal of rehabilitation research and development.* 2016;53(1):25-36.
17. Macey TA, Weimer MB, Grimaldi EM, Dobscha SK, Morasco BJ. Patterns of care and side effects for patients prescribed methadone for treatment of chronic pain. *Journal of opioid management.* 2013;9(5):325-333.
18. Nguemeni Tiako MJ, Mszar R, Brooks C, 2nd, et al. Cardiac Surgeons' Treatment Approaches for Infective Endocarditis Based on Patients' Substance Use History. *Seminars in thoracic and cardiovascular surgery.* 2020.

19. Becker WC, Gordon KS, Edelman EJ, et al. Are we missing opioid-related deaths among people with HIV? *Drug and alcohol dependence.* 2020;212:108003.

20. Edelman EJ, Gordon K, Becker WC, et al. Receipt of Opioid Analgesics by HIV-Infected and Uninfected Patients *J Gen Intern Med.* 2013;28(1):82-90.

21. Britton MC, Ouellet GM, Minges KE, Gawel M, Hodshon B, Chaudhry SI. Care Transitions Between Hospitals and Skilled Nursing Facilities: Perspectives of Sending and Receiving Providers. *Jt Comm J Qual Patient Saf.* 2017;43(11):565-572.

22. Rosenberg A, Campbell Britton M, Feder S, et al. A taxonomy and cultural analysis of intra-hospital patient transfers. *Res Nurs Health.* 2018.

23. Feder SL, Britton MC, Chaudhry SI. "They Need to Have an Understanding of Why They're Coming Here and What the Outcomes Might Be." Clinician Perspectives on Goals of Care for Patients Discharged From Hospitals to Skilled Nursing Facilities. *J Pain Symptom Manage.* 2018;55(3):930-937.

24. Minges KE, Campbell Britton M, Clark BW, Ouellet GM, Hodshon B, Chaudhry SI. Hospital Readmission From Skilled Nursing Facilities (SNFs): Perspectives of Hospital and SNF Providers. *J Am Med Dir Assoc.* 2019;20(8):1050-1051.

25. Campbell Britton M, Hodshon B, Chaudhry SI. Implementing a Warm Handoff Between Hospital and Skilled Nursing Facility Clinicians. *J Patient Saf.* 2019;15(3):198-204.

26. Germack HD, Fekieta R, Campbell Britton M, Feder SL, Rosenberg A, Chaudhry SI. Cooperation and conflict in intra-hospital transfers: A qualitative analysis. *Nurs Open.* 2020;7(2):634-641.

27. Campbell Britton M, Petersen-Pickett J, Hodshon B, Chaudhry SI. Mapping the care transition from hospital to skilled nursing facility. *J Eval Clin Pract.* 2020;26(3):786-790.

28. Schwartz JI, Gonzalez-Colaso R, Gan G, et al. Structured interdisciplinary bedside rounds improve interprofessional communication and workplace efficiency among residents and nurses on an inpatient internal medicine unit. *J Interprof Care.* 2021:1-8.

29. Chilakamarri P, Finn EB, Sather J, et al. Failure Mode and Effect Analysis: Engineering Safer Neurocritical Care Transitions. *Neurocrit Care.* 2021.

30. Harris MTH, Peterkin A, Bach P, et al. Adapting inpatient addiction medicine consult services during the COVID-19 pandemic. *Addiction science & clinical practice.* 2021;16(1):13.

31. Weimer MB, Guerra M, Morrow G, Adams K. Hospital-based Buprenorphine Micro-dose Initiation. *Journal of addiction medicine.* 2020.

32. Englander H, Weimer M, Solotaroff R, et al. Planning and Designing the Improving Addiction Care Team (IMPACT) for Hospitalized Adults with Substance Use Disorder. *Journal of hospital medicine.* 2017;12(5):339-342.

33. Serota DP, Kraft CS, Weimer MB. Treating the Symptom but Not the Underlying Disease in Infective Endocarditis: A Teachable Moment. *JAMA internal medicine.* 2017;177(7):1026-1027.

34. Englander H, Mahoney S, Brandt K, et al. Tools to Support Hospital-Based Addiction Care: Core Components, Values, and Activities of the Improving Addiction Care Team. *Journal of addiction medicine.* 2019;13(2):85-89.

35. Ackerman AL, O'Connor PG, Doyle DL, et al. Association of an Opioid Standard of Practice Intervention With Intravenous Opioid Exposure in Hospitalized Patients. *JAMA internal medicine.* 2018;178(6):759-763.