Cover Page for Clinical Trials Document Posting

Official Title: Initiating Substance Use Disorder Treatment for Hospitalized Opioid Use Disorder Patients (ISTOP)

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Description: ISTOP Study Protocol with Statistical Analysis Plan (SAP)

Detailed Protocol

Title: Initiating Substance use disorder treatment for hospitalized opioid use disorder patients: A randomized trial of recovery coaches.

Version Date: 09/04/2020

I. Background:

Hospitalizations may be important opportunities to engage opioid use disorder (OUD) patients: Patients with OUD are susceptible to a variety of medical, psychiatric, and social complications, and utilize acute health services at a rate nearly 7 times as many as those without OUD.[1,2] Hospitalizations related to OUD have increased dramatically in the context of the national opioid crisis.[3,4] Due to the complex nature of the co-morbidities, their need for acute medical care is enormous. In a study of 58,243 Medicaid patients in New York State with a drug use disorder, 37.5% of HIV-negative individuals had at least one hospitalization in that year, with an average of 24.5 inpatient days.[5] OUD patients' admissions incur 2.5 times the financial charges as compared to patients without OUD.[6] Once discharged, patients with substance use disorders (SUD) are readmitted at much higher rates than those without a SUD.[7–9] Given the frequency in which OUD patients access hospital care, hospitalizations represent an important opportunity to engage these patients into SUD treatment and avoid readmissions once in the community.[10]

Screening, brief intervention, and referral to treatment (SBIRT) is insufficient to engage out-of-treatment OUD patients: A large majority (90%) of individuals with active SUD are not engaged with any formal treatment.[11] For OUD patients, the shortage of physicians willing to prescribe buprenorphine is a contributing factor.[12,13] A promising approach so far in engaging out-of-treatment SUD patients has been Screening, Brief intervention, and Referral to Treatment (SBIRT).[14–18] SBIRT uses universal and opportunistic screenings for substance use in medical settings using validated tools (i.e. AUDIT-C[19]), followed by a brief intervention and/or referral to treatment, making it one of the highest-ranking preventative services offered in general health care settings.[20–22] However, in contrast to its efficacy in at-risk drinkers, studies of SBIRT for out-of-treatment drug users have been largely negative.[23–28] Therefore, SBIRT alone is insufficient in reducing drug use in hospitalized patients, and clinicians and researchers need to look at interventions that focus on engagement with SUD treatment, initiation of medication-assisted treatment, or lengthier interventions.[7,28]

Initiation of buprenorphine for hospitalized OUD patients is feasible but not enough: Medication-assisted treatment with buprenorphine is almost always initiated in the outpatient setting.[29–31] Indeed, only a small fraction (10.7-16.7%) of patients admitted for an opioid-related issue received any FDA-approved OUD medication within 30-days of discharge.[32,33] Delaying the initiation of treatment places hospitalized patients at very high risk for relapse immediately after discharge. Studies have documented the feasibility of initiating buprenorphine during hospitalization.[34–37] In our previous study of 47 hospitalized OUD patients initiated on buprenorphine, 46.8% successfully continued treatment following discharge.[35] In another study of 145 hospitalized OUD patients randomized to either initiation of buprenorphine and linkage to treatment (intervention) or buprenorphine detoxification alone (control), those in the intervention arm were significantly more likely to continue outpatient treatment (72.2% vs 11.9%).[34] However, by 6 months after discharge, only a small proportion of those subjects in either arm remained in treatment (16.7% intervention vs 3.0% control). In a randomized trial of 329 OUD patients in the emergency room, subjects received 1) screening and referral [referral], 2) screening, brief intervention, and referral [brief intervention], or 3) screening, brief intervention, and initiation of buprenorphine [buprenorphine]. Those initiated on buprenorphine, compared to those who were not, were significantly more likely to be engaged with buprenorphine treatment

following discharge (78% [buprenorphine] vs 45% [brief intervention] vs 37% [referral], p<0.001).[37] However, the rate of opioid negative urines at 30 days did not differ significantly across the 3 groups. These results suggest that initiation of buprenorphine in acute care settings facilitate linkage to outpatient treatment. However, because patients face numerous internal and external barriers to remaining engaged with treatment and reducing illicit opioid use, a more intensive intervention that continues into the community may be needed.

Interventions that improve transitions of care tailored to OUD patients are needed to reduce readmissions: In the US, almost 20% of all hospitalized patients are readmitted within 30 days after discharge, and close to half are readmitted within 6 months.[38] High rates of avoidable 30-day re-admission rates can result in financial penalties for the hospital.[38,39] To improve the transitions of care between the hospital and outpatient treatment, interventions that address the following domains appear to be most effective in reducing readmissions: 1) monitoring and managing symptoms, 2) educating and promoting self-management skills, and 3) enlisting social and community supports.[40–43] Even though SUD patients, compared to those without, are 1.5 times more likely to be re-admitted due to their complex biopsychosocial needs, research to reduce readmissions has not focused on SUD patients.[7–9,44] In a randomized trial of 749 hospitalized patients, a nurse helped plan and coordinate the discharge, while a pharmacist provided a telephone follow-up to provide education and support.[45] The intervention reduced readmissions (0.695, 95% CI, 0.515 to 0.937), but patients with drug use disorders still had twice the odds of readmission (1.97, 95% CI, 1.06 to 3.63).[7] Given that drug using patients receiving regular SUD treatment can experience a 15% reduction in subsequent hospitalizations, more research is needed with interventions tailored specifically for OUD patients.[5]

Care management may be needed during transitions of care to educate and support hospitalized OUD patients: Care management interventions are designed to meet the needs of individual patients by helping to manage their medical conditions more effectively, showing promise with a variety of illnesses including SUD. [46–54] In an 8-week study of dual diagnosis patients, 102 veterans being discharged from an inpatient psychiatrist facility were randomized to an intervention delivered by a care manager and a peer support specialist (recovery coaches), or to a matched attention control consisting of health education sessions.[55] The care manager helped with treatment planning following discharge, encouraged adherence to treatment, and educated about addiction and relapse prevention skills. Those in the intervention arm were more likely to be engaged with outpatient treatment at 8 weeks than compared to control subjects (44 vs 22%, p<0.01). Given the complex medical and psychosocial needs of hospitalized OUD patients, more research on care management interventions that focus on the transitions of care for OUD patients is needed.

Recovery coaches (i.e. peer-driven recovery supports) may be necessary to support OUD patients in the community: There is a growing body of evidence for the benefits of recovery coaches, who provide peer-delivered support services, to help SUD patients in the community.[55–63] Tracing their origin to mutual support groups to supplement traditional clinical services, recovery coaches are individuals with lived experience of recovery, and are referred to by a variety of names in the literature (i.e. consumer providers, peer support specialists, peer workers/mentors). Recovery coaches typically provide services in four domains: 1) emotional (demonstrate empathy, bolster confidence, and foster hope), 2) informational (share knowledge and help skill-building), 3) instrumental (provide assistance with housing, employment, transportation, etc.), and 4) affiliational (create community and sense of belonging).[57] Studies of recovery coaches have demonstrated greater treatment retention, reduced substance use, and reduced inpatient utilization.[59,62,55,63,64] However, no prior studies have examined the impact of recovery coaches in improving buprenorphine treatment retention.

The proposed project addresses these unmeet needs by testing a novel intervention to improve the treatment of OUD patients hospitalized for medical reasons. The intervention will

combine 1) medication-assisted treatment with buprenorphine initiated in the hospital, 2) care management to address domains known to improve transitions of care (monitoring and managing symptoms, encouraging self-management skills, and enlisting community and social supports[40–43]), and 3) recovery coaches to assist the patient in the community after discharge from the hospital. Previous studies lacked one or more of these components, or were not focused on OUD patients. While the use of buprenorphine has been studied with hospitalized patients, previous studies did not provide longitudinal support in the community following discharge.[34,36] Previous studies on transitions of care have not specifically targeted hospitalized OUD patients, even though drug use is a well-known risk factor for readmissions.[7] Care management has been frequently utilized to manage complex patients, but no prior studies have targeted hospitalized OUD patients being discharged into the community. Finally, recovery coaches have also not been studied to improve treatment retention of OUD patients treated with buprenorphine[59]. In this study, the trainings and responsibilities of the recovery coach and care management will be merged into one role. Further, this study brings these promising elements together into one novel model. If successful, this model could prove useful for engaging hospitalized out-of-treatment OUD patients.

II. Aims:

Our hypothesis is that the recovery coach intervention will be associated with greater success not only in remaining in treatment, but also in reducing the likelihood of hospital readmissions.

Specific Aim #1: To assess whether subjects randomized to the recovery coach intervention will demonstrate greater retention in treatment and better opioid use outcomes at 24 weeks compared to control subjects in a randomized controlled trial.

Hypothesis 1a: Subjects receiving the intervention will be more likely to remain in treatment at 24 weeks, as compared to control subjects.

Hypothesis 1b: Subjects receiving the intervention will report fewer days of illicit opioid use in the prior 30 days at 24 weeks, as compared to control subjects.

Specific Aim #2: To assess whether subjects receiving the intervention will demonstrate fewer hospital readmissions at 24 weeks compared to control subjects in a randomized controlled trial.

Hypothesis 2: Subjects receiving the intervention will report fewer hospital readmissions at 24 weeks compared to control subjects.

III. Subject selection:

Inclusion criteria:

- English speaking, adults aged 18-75
- DSM-5 opioid use disorder, severe, actively using illicit opioids until the time of hospitalization
- Have a working telephone
- Can identify at least 2 individuals who can act as points of contact following discharge from the hospital
- Willing to engage in treatment (either a psychosocial treatment program AND/OR any medication treatment with methadone or buprenorphine)
- In SUD treatment for less than 6 months and/or not currently in treatment

Exclusion criteria:

- Liver function test >3x upper normal limit
- Pregnant
- Psychotic disorder, active suicidality or homicidality

- Condition likely to be terminal in 24 weeks such as cancer
- Unable to perform consent due to mental status

IV. Subject enrollment:

Recruitment will be conducted at BWH and BWFH. Study population will include hospitalized OUD patients currently not engaged in any outpatient SUD treatment, and who are willing to engage in treatment (either a psychosocial treatment program and/or any medication treatment with methadone or buprenorphine). The electronic medical record will be programmed to produce a daily report of any patient with OUD admitted to the inpatient medical units. This program will utilize a natural language processing algorithm, which will use medical records to find patients with OUD who are not currently on buprenorphine but may be candidates for it (and therefore also potentially eligible for the study). Because the algorithm will need to be trained to correctly identify potential patients based on inclusion/exclusion criteria, there will also be a non-intervention/non-interaction group, specifically patients who do not have OUD (and thus would not be potential subjects for recruitment). The data from these patients would be obtained via RPDR, with the sole purpose of training the algorithm and confirming that it is indeed correctly excluding ineligible subjects based on our inclusion/exclusion criteria. Hospitalists will also be informed of the study to help identify additional patients to be approached. Finally, all patients with OUD who are referred for an addiction consultation, and willing to engage in treatment after discharge will be approached for possible inclusion.

Either the primary medical team or the addiction psychiatry team will first inform the patient about the study. If the patient expresses interest and consents to be approached by the study staff, the research assistant will be notified. The research assistant will first ask the patient's inpatient nurse about the appropriateness of approaching the patient. Once the nurse agrees that the patient can be approached, the research assistant will provide further information to the patient about the study. The patient will also be provided with a flyer that provides a concise summary of the study to allow ample time for patients to consider the study.

Due to the COVID-19 pandemic, and as this is a minimal risk study, we also propose an option for remote consenting for the duration of the public health emergency. As the research assistant will only be allowed on-site for a limited number of days each week, there is a possibility that part of the enrollment or consenting process will have to happen remotely before the subject is discharged. In this case, all preceding recruitment procedures will remain the same; either the primary medical team or the addiction psychiatry team will inform the patient about the study and ask whether the patient consents to be approached by the study team. If the patient consents, the research assistant will introduce the study, answer questions, determine preliminary study eligibility, and allow ample time for the patient to consider whether to enroll. The research assistant will also leave a physical copy of the Research Study Fact Sheet, the informed consent form, and the "Notification of Changes due to COVID-19" general information sheet. These will be for the patient to keep and review in case the research assistant is unable to return for an in-person follow-up to review and sign the consent form, after the patient has had time to consider the study. In the case that enrollment will continue remotely, the research assistant will call the participant to conduct the consent discussion, and then subsequently randomize the participant and conduct the baseline measures remotely via phone. Since this is a minimal risk research study, the remote process would use a verbal consent process which requires waiver of informed consent documentation (no signature will be obtained on the consent document).

A study staff will approach potential participants to determine preliminary study eligibility. Based on prior studies of this population, we expect OUD patients to have the following characteristics: 50% male, 70% Caucasian, 40% with prior heroin use, admission diagnosis of acute pain (40%) and infection (20%), length of stay of 11 days, and 80% needing opioid

analgesia. At the initial screen, all eligible English-speaking OUD patients will be offered a referral to methadone treatment and informed about the trial. Extended-release naltrexone, which requires that all opioids be stopped 7-10 days prior to initiation, will not be offered because the vast majority of patients screened will have received opioid analgesic during the hospitalization. As such, most potential patients would not be able to initiate naltrexone prior to discharge. Initiation of buprenorphine will be considered for patients who are medically stable enough to undergo induction, have an interest in initiating buprenorphine maintenance treatment, and have no medical or surgical contraindications. The full inclusion and exclusion criteria will then be applied.

V. Study procedures:

Randomization: After informed consent is given, participants will be randomized using a computerized random number generator with numbers in sealed envelopes in study binders.

Interventions:

Control group: Participants in the control arm will receive treatment-as-usual at our hospital. All participants will receive a thorough psychosocial evaluation to help with discharge planning. Following initiation of buprenorphine or methadone, the addiction social worker will provide the participant with the intake number for the BWH-affiliated buprenorphine programs, or contact information for relevant methadone programs. Patient preference due to geographic considerations will be taken into account when choosing the clinic to which participants are

Table 2: Components of the ISTOP intervention

In-hospital component (adapted from MISSION manual)

Session #1: (90 minutes with Recovery Coach)

1) Introduce recovery coach, and review overall intervention
2) Complete a psychosocial needs assessment
3) Create a provisional treatment plan based on identified service needs and prioritizing of goals.
4) Refer to BWH/BWFH-affiliated buprenorphine clinic
5) Use motivational interviewing to increase motivation for treatment
6) Review the following areas:
   - A. Monitoring and managing symptoms:
     - Review importance of buprenorphine adherence in managing cravings and preventing relapse.
     - Help identify cravings and warning signs of relapse
   - B. Patient education and self-management:
     - Educate about addiction and role of buprenorphine.
     - Review relapse prevention skills to cope with high-risk situations, cravings, and negative emotions
   - C. Enlisting community and social supports:
     - Encourage self-help group attendance
     - Review importance of establishing a support system

Session #2: (60 minutes with Recovery Coach)

1) Review treatment plan
2) Organize post-discharge appointments and problem-solve potential barriers in keeping appointments.
3) Reconcile discharge medication regimen.
4) Review the use of naloxone overdose rescue kit.
5) Invite family members to attend session if applicable.
6) Notify treatment plan to outpatient providers if applicable.

Post-discharge component (adapted from MISSION manual)

Recovery coach (2-3 hours per week of direct contact)

1) Assist implementing Treatment Plan and help prioritize goals
2) Weekly coach-led sessions utilizing the ISTOP treatment manual
   - Brief introduction to day's topic
   - Offer personal insights or a story to further setup topic
   - Questions, if needed, to spark discussion
   - A facilitated discussion on the topic
3) Provide support in the following areas:
   - A. Monitoring and managing symptoms:
     - Encourage continuation of buprenorphine treatment
     - Accompany participants to appointments
     - Liaison between participants and clinicians
   - B. Patient education and self-management:
     - Help determine and increase motivation for recovery goals
     - Share and suggest coping strategies
     - Reinforce relapse prevention skills
     - Recreational planning and modeling healthy living
   - C. Enlisting community and social supports:
     - Role modeling and inspiring hope
     - Provide support during crises or job stresses
     - Identify and link to community recovery programs
     - Assist with essential life skills such as setting up bank accounts, getting a driver's license, using public transit, etc

referred. The participants will be encouraged to schedule an appointment prior to discharge. Instructions on safely tapering the buprenorphine will be reviewed prior to discharge, in the event the participant does not initiate treatment before the prescription runs out. Participants will be provided with community resources including outpatient addiction programs, 12-step meetings, and referral to outpatient mental health treatment if needed. We recognize that the control group does not balance non-specific effects of the intervention (e.g. increased attention). If our finding is promising, this study will help inform better control group design to account for non-specific effects of the intervention.

ISTOP intervention group: The intervention arm will include in-hospital and post-discharge components (**Table 2**). Both components will be adapted from the MISSION-VET manual[68] under supervision from the mentors to be used for the ISTOP treatment manual. The candidate and recovery coaches will meet weekly to review all participants in the study. If the participant is re-hospitalized during the study period, the team will remain engaged with the patient, and the in-hospital component of the intervention repeated if the hospitalization occurs at BWH or BWFH.

In hospital component: There will be 2 sessions during the hospitalization, unless the patient is being discharged imminently, in which case both sessions will be completed at the same time (**Table 2**). Due to the COVID-19 pandemic, all recovery coach visits (both "in-hospital" and post-discharge) will occur remotely (either via phone or Partners Enterprise Zoom) until further notice. During the first session, the recovery coach will review goals of the intervention, complete a psychosocial needs assessment, and create a provisional treatment plan based on identified service needs. Following initiation of buprenorphine or methadone, the addiction social worker will provide the participant with the intake numbers for the BWH-affiliated buprenorphine programs and contact information for any relevant methadone programs. Patient preference due to geographic considerations will be taken into account when choosing the clinic to which participants are referred. The participants will be encouraged to schedule an appointment prior to discharge. The importance of continuing treatment will be reinforced. The recovery coach will focus on monitoring and managing symptoms, educate about the nature of recovery and relapse prevention skills, and reinforce the importance of community and social supports. The MISSION-VET manual, which covers the above elements, will be used to manualize the recovery coach intervention while in the hospital.[68] During the second session, the Recovery Coach will review the treatment plan, organize post-discharge appointments, reconcile medications, and provide naloxone rescue training. If applicable, family members will be encouraged to be present for all in-hospital sessions.

Post-discharge component: Following discharge, the recovery coach will meet with the participant up to 3 hours per week (**Table 2**). Each recovery coach will carry a caseload of no more than 3 participants at a time. More frequent contact will be permissible if the care team needs to respond to emergencies or other clinical issues requiring additional contacts. For participants who may live outside of Boston or are otherwise unable to return to the Brigham Hospital area, the recovery coach will meet with participants via phone call or video conferencing. Each week, the coaches will conduct peer-led individual sessions using topics adapted from the MISSION-VET manual. The recovery coaches will encourage the continuation of treatment and accompany participants to appointments if necessary, and function as a liaison between the participant and the clinicians. The coaches will help determine recovery goals, share and suggest coping strategies, and model healthy living. The coaches will also instill hope through example, and provide support during crises. The coaches will assist with linkage to community programs, and assist with essential life skills such as setting up a bank account or using public transportation. The candidate will meet

weekly with the recovery coaches to review each case. If the participant successfully linked with the BWH-affiliated buprenorphine clinic, retention in treatment will be confirmed with the clinic.

Fidelity: The MISSION Fidelity Index from the MISSION-VET manual[68] will be adapted for this study to ensure intervention fidelity. The index is designed to document services delivered as indicated in the manual.
Compensation: Participants will be reimbursed $50 for the baseline, 4- and 12-week follow-up visit, and $100 for the 24-week visit.

Schedule of Assessments: Baseline measures will be obtained during the hospitalization. Follow up assessments will occur at 4, 12 and 24 weeks after discharge. A research assistant blinded to study assignment will collect all data. Patients who are unable to return to the hospital for the follow-up assessments will complete their measures via phone call or Partners Enterprise Zoom (if participant prefers) with the research assistant.
Measures: As recommended by notice NOT-DA-12-008, measures from the Substance Abuse and Addiction Collection of the PhenX Toolkit were chosen where appropriate. The schedule of assessments is summarized in **Table 3**.

- Demographic measures (Core Tier 1 measures): A questionnaire to collect demographic information on age, gender, ethnicity, marital status, employment, housing, education, and socioeconomic status.
- Mini-International Neuropsychiatric Interview (MINI)[72]: A brief structured psychiatric diagnostic interview that was designed to permit the rapid diagnosis of the major psychiatric disorders.
- Pregnancy test: Females will undergo pregnancy testing at the time of screening.
- Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES)[74]: To assess readiness.
- Urine toxicology: Routine urine immunoassay screen will be obtained to assessed, including opioids. These will be obtained during routine clinical visits, separate from study visits.
- Addiction Severity Index 5th edition (ASI)[75]: The ASI will assess multiple dimensions of SUD.
- Opioid craving[76,77]: A single-item questionnaire will be used to determine craving for opioids.
- Patient Health Questionnaire 9-item (PHQ9)[78]: This questionnaire will assess depressive symptoms.
- Brief Pain Inventory[79]: Pain severity and the degree to which pain interferes with life will be assessed.
- Time-line follow back (TLFB)[81]: Assess past 30-day use of substances.
- Verification of treatment retention: Treatment retention will be verified by the BWH/BWFH-affiliated clinic.
- The Health-Care Climate Questionnaire - Recovery Coach version (HCCQ-RC): A brief 15-item measure added to assess patients' perceptions of the degree to which they experience their recovery coach to be autonomy supportive.
- Adverse Childhood Experiences International Questionnaire (ACE-IQ): A survey designed to collect information from adults about events they experienced in the first 18 years of their lives, including family dysfunction and exposure to violence.
- Health-Care Climate Questionnaire – Hospital Care Team Version (HCCQ-HCT): A brief 15-item measure added to assess patients' perceptions of the degree to which

they experienced the hospital care team (e.g. nurses, doctors, social workers) to be autonomy supportive.

- PTSD Checklist (PCL-5): A 20-item self-report measure that assesses the presence and severity of PTSD symptoms, corresponding with DSM-5 criteria for PTSD.
- Brief Addiction Monitor (BAM): A 17-item, progress-monitoring instrument for patients in treatment for a substance use disorder, used to assess risk factors for substance use, protective factors that support sobriety, and drug and alcohol use.
- Short Form 12 health survey (SF-12): A short 12-item survey that assesses mental and physical functioning as well as overall health-related quality of life.

	Screening	Baseline	4 weeks	12 weeks	24 weeks
Demographics	X				
MINI	X				
Pregnancy Test	X				
Readiness to Change	X				
Liver function tests	X				
ASI		X	X	X	X
Opioid cravings		X	X	X	X
PHQ9		X	X	X	X
BPI		X	X	X	X
TLFB		X	X	X	X
Verification of Treatment					
HCCQ-RC		X	X	X	X
ACE-IQ		X			
HCCQ-HCT		X			
PCL-5		X	X	X	X
BAM		X	X	X	X
SF-12		X	X	X	X

Table 3: Schedule of measures

Project Timeline: The first 8 months of Year 1 will be devoted to hiring of the study staff, the intervention manual development, staff training, pilot-testing the protocol with 2 participants, and protocol refinement. During the intervention period, 6 patients will be screened for potential enrollment every month, enrolling 2 participants per month on average for 30 months, concluding by the beginning of Year 4. Manuscript submission will begin in Year 1. Year 4-5 will be devoted to data analysis, and submission of an R01 grant application (**Table 4**).

Anticipated problems:

Slow recruitment: If recruitment does not proceed as planned, we will increase outreach to hospitalists to help identify potential participants admitted to BWH and BWFH inpatient medical unit.

Adjustments to the intervention: The first 2 participants will function as pilot cases to identify any problems with the study intervention. Appropriate adjustments to the standard operating procedures, recruitment, manual adaptation, and measures will be made according to these

2 pilot cases. Because the study procedures will be adapted from the MISSION manual, an established treatment manual, 2 participants should be sufficient to assess the need for modifications.

VI. Biostatistical analysis:

Sample size/power analysis: In a study of a care management intervention for patients with substance use disorder in primary care, individuals receiving the intervention were more likely to remain in treatment at 24 weeks (40% vs 10%).[52] While this study is entirely community based, no other comparable studies have been conducted with OUD patients on buprenorphine. Based on this effect size, we plan to screen 145 participants, assuming a 60% attrition due to screening failure, allowing for a sample size of 58 available for analysis, evenly divided between the control and intervention arm. This will yield a statistical power of 0.8 and 95% confidence level to detect differences in proportions of participants who remain in treatment at 24 weeks, as confirmed by the BWH-affiliated clinic. The study will not be powered to detect smaller effect sizes, but will be helpful in providing important information about effect sizes to adequately power future studies.

Specific Aim #1: The hypothesis that participants receiving the intervention will be more likely to remain in buprenorphine treatment at 24 weeks will be tested using logistic regression, treating the endpoint as a categorical variable. Treatment retention data will be obtained directly from the BWH/BWFH affiliated buprenorphine clinics. The hypothesis that participants receiving the intervention will report fewer days of illicit opioid use at 24 weeks will be tested using mixed effects ANOVA modeling, treating the endpoint as a continuous variable. ANCOVA will be used to adjust for relevant covariates, including age, sex, ethnicity/race, and baseline illicit opioid use. Illicit opioid use will be determined from the TLFB and urine toxicology results.

Specific Aim #2: The hypothesis that participants receiving the intervention will be less likely to be readmitted at 24 weeks will be tested using logistic regression, treating the endpoint as a categorical variable. Readmission data will be obtained from the ASI and GAIN service utilization items.[80] Results will be adjusted for relevant covariates, including demographic variables and baseline clinical variables. While 30-day readmission rate is an important metric for hospitals, the readmission rate at 24 weeks may better evaluate the impact of the proposed intervention.

Missing data: Extensive efforts will be made to avoid missing data by vigorous outreach. Missing data on treatment continuation or retention will be imputed as treatment discontinuation (i.e. participant did not continue or remain in treatment). Missing urine toxicology samples will be treated as positive for illicit opioid use. Data on possible reasons for missing observations will be collected so that missing data mechanism may be appropriately modeled statistically. Using methods to manage missing data, results will be compared to the original dataset to identify any discrepancies and verify conclusions.

VII. Risks and discomforts

The well being of the study participants is of utmost importance. The in-depth screening procedure has been designed to ensure that individuals with any underlying medical or psychiatric illness are identified that may place them at greater risk for experiencing adverse effects during the study. The study procedures are designed to be minimally invasive and associated with minimal risk. Alternative procedures with lower risk are not available. Nevertheless, the protocol raises several areas of concerns: confidentiality, emotional distress, suicidal ideation, buprenorphine medication, intoxication, and overdose.

Confidentiality: Confidentiality is of utmost importance given the sensitive nature of the illness and data collected. During research there is always a possibility for a breach of confidentiality, which may potentially cause personal, social, occupational, legal, and other harm. Our research team is very aware of the importance of maintaining strict confidentiality and has prior experience dealing with sensitive information. The following precautions will be used to protect the privacy of participants and maintain confidentiality of research data: all staff will be trained in confidentiality and data security procedures; privacy will be maintained by conducting all study procedures in private hospital rooms or in close, sound-proof rooms; data will be de-identified and coded with unique ID numbers; data will be securely stored in locked filing cabinets in locked rooms; electronic data will be stored in password protected documents located on password protected computers and secure servers; the key linking participants names and ID numbers will be stored in a separate password protected document in a password protected computer; access to data storage areas will be restricted to authorized study personnel; and all analysis will be conducted on de-identified data. While breach of confidentiality is possible, these safeguards will ensure that such a breach will be highly unlikely.

Emotional distress: Some patients may experience discomfort or embarrassment related to providing urine samples or answering questions about substance use and other personal behaviors. They could also experience unexpected encounters with friends or associates while in the study. However, based on prior studies with this population, we expect the degree of distress to be very limited. All research personnel will be extensively trained on study procedures, including the conduct of the interviews that elicit personal information, and the importance of being sensitive to and respectful of all participants. In cases where emotional distress does occur, research personnel will be trained on how to identify and address it, and when to terminate an interview. Multiple levels of back-up support for research personnel will be developed. The candidate is a board certified psychiatrist, and will be able to ensure that appropriate services are received.

Suicidal ideation: Patients with OUD frequently have psychiatric co-morbidities, namely depression. Participants who disclose any suicidal ideation during the study (either through self-report during an assessment or self-reported on the PHQ-9) will be addressed appropriately and with sensitivity. Any disclosures will be handled within existing legal mandates, clinical practice, and social norms. Consistent with standard clinical practice, when possible, disclosures will be discussed with the participant to determine the best management options. This may include notifying the inpatient/outpatient providers or family members, referring to medical treatment, calling emergency services, or escorting the participant to the Emergency Room at Brigham and Women's Hospital. When required by law, the police department will be notified. The candidate is a board certified psychiatrist and has extensive experience managing acutely distressed patients with mental or substance use disorders.

Buprenorphine medication safety: All subjects in the trial will be started on buprenorphine prior to randomization, and will be deemed appropriate for the medication by consensus of the treating physicians and a buprenorphine-waived physician on the addiction consultation-liaison team. Buprenorphine has been tested extensively and is FDA-approved for the treatment of OUD. Indeed, medication-assisted treatment (with buprenorphine, methadone or naltrexone) is the standard of care for the treatment of OUD. Because buprenorphine is a partial mu-opioid agonist, the medication can in some individuals cause intoxication, especially if used intravenously. As such, only the combination tablet that contains naloxone will be used, unless the participant has a documented allergy to naloxone. The combination tablet will produce a clinically significant opioid withdrawal if injected. All participants will be told of this reaction, and will also be asked to refrain from injecting the medication. Buprenorphine can also cause a mild euphoria and respiratory depression, but much less than compared to full agonists. Subjects will be monitored during the hospitalization to ensure they can adequately tolerate the

medication. Commonly reported side effects include nausea, vomiting, constipation, muscle cramps, insomnia, irritability, sweating, and fevers. Subjects will be asked to report any side effects to the study staff, hospital staff, or their buprenorphine prescriber. If these side effects are reported to study staff, the candidate will be informed and will take appropriate action. The candidate has extensive experience managing OUD patients with buprenorphine, and is well versed in the appropriate clinical management of any emergent side effects from buprenorphine. Subjects will also be advised that ingesting buprenorphine with other sedative drugs, such as benzodiazepines, dramatically raises the possibility for a synergistic reaction that can cause an overdose or even death. Individuals with any underlying liver disease or have a history of hepatitis C will be informed that buprenorphine use has been rarely associated with liver failure, and that liver function test will be obtained. Subjects will be informed that buprenorphine medication should be stored in a secure location, ideally with a lock-box, to ensure no one else can access the medication including children. Finally, studies show that after stopping buprenorphine medication, individuals are at heightened risk of relapse to illicit opioid use, as well as greater likelihood of non-fatal and fatal overdoses. As such, subjects will be counseled about the risks of relapse and overdose throughout the study period.

Intoxication: The study population targets OUD patients, who were actively using illicit opioids prior to the hospitalization. As such, it is possible for participants to be intoxicated from illicit opioids or other substances during the their work with recovery coaches or during study visits. Participants will be required to abstain from substances other than buprenorphine for at least 4 hours prior to each study visit. Intoxication will be determined through self-report and clinical observation. If a participant is intoxicated in any way, they will not be permitted to complete the visit, and the visit will be rescheduled at the earliest convenient time. Consistent with standard clinical practice, when possible, the recovery coaches will discuss with the candidate to determine the best management options. This may include notifying the inpatient/outpatient providers or family members, referring to medical treatment, calling emergency services, or escorting the participant to the Emergency Room at Brigham and Women's Hospital.

Overdose: Patients with OUD are at heightened risk from fatal and non-fatal overdoses during and after buprenorphine treatment, especially if using alcohol or sedative drugs such as benzodiazepines. As such, participants will be required to abstain from using these substances. However, given their underling illness, some participants may still ingest these other substances during the study period. All study staff, including recovery coaches, and all participating subjects will be trained in the recognition and initial management of an overdose using the naloxone-rescue kits. Subjects will also be asked to identify family or supports that can carry the naloxone rescue kits. The candidate is a board certified addiction psychiatrist well versed in the recognition and management of overdoses, and appropriate clinical action will be taking in the event of an overdose. In addition, all recovery coaches will be receive training on overdose prevention and the use of naloxone rescue kits.

VIII. Potential benefits:

The risk/benefit ratio for this study is relatively low, primarily because the intervention and the data collection procedures are minimally invasive. An extensive screening procedure will ensure that individuals entering the trial will have no contraindications. Trained research personnel will perform all study procedures to minimize risks, discomforts, and adverse effects. Buprenorphine treatment is a FDA-approved treatment for the treatment of OUD, and reduces illicit opioid use and related morbidities associated with opioid use disorders. The recovery coaching intervention may provide benefit to the study participants by increasing their likelihood of remaining in treatment, reducing their illicit opioid use, and reduce hospital readmissions.

This study will generate valuable information about the effect of combining recovery coaches with buprenorphine initiated during hospitalization. The results will help inform the direction needed to take in developing effective strategies to improve the care of hospitalized OUD patients. Given the potential public health impact, and the minimal risk associated with participation, we believe that the risk to participants is reasonable.

IX. Monitoring and quality assurance:

1. **Data Quality and Management**
    - **a.** Description of plan for data quality and management: The PI or study staff will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol. To minimize any conflicts of interest, a physician from Brigham and Women's Hospital familiar with clinical research who is not a collaborator or investigator on the proposed project, nor a close colleague, will serve as an independent individual to monitor the data and safety.
    - **b.** Frequency of review: The candidate will complete reports every 3 months detailing the study progress and subjects' status, any adverse events, and any protocol deviations, which will be submitted to the independent individual for review.
2. **Subject Accrual and Compliance**
    a. Measurement and Reporting of Subject Accrual, Compliance with inclusion/exclusion criteria: Review of the rate of subject accrual and compliance with inclusion/exclusion criteria will occur every 3 months to ensure that a sufficient number of participants are being enrolled and that they meet eligibility criteria and the targeted ethnic diversity goals outlined in the proposal.
    b. Measurement and reporting of participant adherence to treatment protocol: Data on adherence to the treatment protocol will be collected weekly by research staff and reviewed quarterly by the PI. Fidelity to the treatment manual will be reviewed by the candidate each week with the recovery coaches.
3. **Justification of sample size:** In a study of a care management intervention for patients with substance use disorder in primary care, individuals receiving the intervention were more likely to remain in treatment at 24 weeks (40% vs 10%). While this study is entirely community based, no other comparable studies have been conducted with OUD patients on buprenorphine. Based on this effect size, we plan to screen 145 participants, assuming a 60% attrition due to screening failure, allowing for a sample size of 58 available for analysis, evenly divided between the control and intervention arm. This will yield a statistical power of 0.8 and 95% confidence level to detect differences in proportions of participants who remain in treatment at 24 weeks, as confirmed by the BWH-affiliated clinic. The study will not be powered to detect smaller effect sizes, but will be helpful in providing important information about effect sizes to adequately power future studies.
4. **Stopping rules:** This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial
5. **Designation of an independent monitor: T**o minimize any conflicts of interest, a physician from Brigham and Women's Hospital familiar with clinical research who is not a collaborator or investigator on the proposed project, nor a close colleague, will serve as an independent individual to monitor the data and safety.

6. **Safety Review Plan**: Study progress and safety will be reviewed monthly (and more frequently if needed). Progress reports, including patient recruitment, retention/attrition, and AEs, will be provided to the Independent Monitor following each of the monthly reviews. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely.
7. **Study report outline for the independent monitor:** Study Report tables will be generated only from aggregate (not by group assignment) baseline and aggregate safety data for the study population. A separate Closed Safety Report, with masked group baseline and safety data, will be generated for the Independent Monitor(s) by a designated unmasked member of the team but will not be reviewed by the study team.
8. **Informed consent:** The subject (if applicable, parent/guardian) will be asked to review the study consent form. The PI or Co-Investigator (Co-I) will meet with the subject to review the form, to confirm the subject's understanding of the study, and to answer any questions the subject might have.Once the subject demonstrates understanding of the study and agrees to participate in the study, the consent will be signed in the presence of the PI (or Co-I) and a witness
9. This study does not involve any medications or devices and carries no risk of harm from such medications or devices.

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