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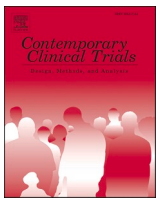

Design and methods of a multi-site randomized controlled trial of an integrated care model of long-acting injectable buprenorphine with infectious disease treatment among persons hospitalized with infections and opioid use disorder

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ABSTRACT

Background: Hospitalization with co-occurring opioid use disorder (OUD) and infections presents a critical time to intervene to improve outcomes for these intertwined epidemics that are typically managed separately. A surge in life-threatening infectious diseases associated with injection drug use, including bacterial and fungal infections, HIV, and HCV accounts for substantial healthcare utilization, morbidity, and mortality.
Infectious Disease (ID) specialists manage severe infections that require hospitalization and are a logical resource to engage patients in medication treatment for OUD (MOUD). An injectable long-acting monthly formulation of buprenorphine (LAB) has a potential advantage for initiating MOUD within hospital settings and bridging to treatment after discharge.
Methods: A randomized multi-site trial tests a new model of care (ID/LAB) in which OUD and infections are managed by ID specialists and hospitalists using LAB coupled with referrals to community resources for long-term MOUD. A sample of 200 adults admitted to three U.S. hospitals for OUD and infections are randomly assigned 1:1 to ID/LAB or treatment as usual (TAU). The primary outcome measure is the proportion of patients enrolled in effective MOUD at 12 weeks after randomization. Secondary outcomes include relapse to opioid use, adherence to infectious disease treatment, infection morbidity and mortality, and drug overdose.
Results: We describe the design, procedures, statistical analysis, and early implementation issues of this randomized trial.
Conclusions: Study findings will provide insight into the feasibility and effectiveness of integrated treatment of OUD and serious infections and have the potential to reduce morbidity and mortality in this vulnerable population.

1. Introduction

Almost a half million Americans have died from opioid overdose since the late 1990's, overtaking motor vehicle accidents as the leading cause of accidental death in the US and reducing overall life expectancy [1,2]. Associated with this staggering toll is a surge in life-threatening infectious diseases related to opioid and injection drug use (IDU), including bacterial and fungal infections [3,4], HIV [5], and HCV [6]

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that account for substantial healthcare utilization, morbidity, and mortality [7]. These intertwined epidemics of addiction and infection are typically managed separately.

Treatment of infectious disease (ID) in patients with opioid use disorder (OUD) is impeded by inadequate treatment of OUD. Hospitalized patients with infections often lack access to clinicians who are trained in medication treatment for OUD (MOUD) provision (e.g. buprenorphine, methadone, extended-release naltrexone) and standard of care typically consists of detoxification and/or referral to outpatient treatment. Detoxification from opioids, a historical standard of care, is associated with a high risk of relapse [8] and overdose [9,10]. In addition, patients may leave 'against medical advice' (AMA) before completion of antimicrobial therapy due to experiencing untreated opioid withdrawal symptoms [11], often leading to readmissions due to inadequate treatment of their infection [12]. Initiation of maintenance treatment with MOUD should be the standard of care as these medications are the most effective treatments for OUD, reducing opioid craving, opioid relapse, overdose and death [13–15]. Despite its extensive evidence base, MOUD are infrequently prescribed in the hospital setting or upon discharge from inpatient admission [16]. ID specialists and hospitalists are a logical resource to engage patients in treatments for both OUD and infections, building capacity and increasing access to MOUD.

Emerging evidence over the past two decades suggests that integration of OUD and infectious disease care improves outcomes [11,17–19]. MOUD improves HIV viral suppression and retention on antiretroviral therapy and reduces acquisition of HCV [20–22]. ID physicians may be first to engage patients with infections and OUD during hospitalization with the unique vantage point of providing inpatient to outpatient continuity of care [23]. Given the scarcity of MOUD providers, they are an efficient resource to provide integrated addiction and infection care while shepherding patients through the vulnerable acute care and post-discharge period [17].

A monthly injectable long-acting formulation of buprenorphine (LAB), recently approved by the FDA (Sublocade®), produces therapeutic blood levels for a month and has advantages for initiating inpatient OUD treatment including: 1) immediate and sustained treatment of opioid craving and withdrawal symptoms which frequently cause patients to leave the hospital prematurely; 2) allowing clinicians treating the infections to initiate early OUD treatment negating the wait for an addiction specialist consultation or deferring treatment to after discharge; and 3) providing a bridge to long-term OUD treatment, reducing relapse and optimizing antimicrobial treatment. LAB formulations have been found to be superior to placebo and non-inferior to SL buprenorphine for treatment of OUD [24,25], however available data for persons with concurrent infections and for patients hospitalized with co-occurring infections are scarce.

This study tests a new model of care (ID/LAB) in which OUD and infections are managed concurrently by ID specialists and hospitalists using LAB, followed by timely referral to community resources for long-term OUD treatment. We describe the design, protocol and outcomes measures in this on-going multi-site randomized controlled trial.

2. Methods

2.1. Study design

COMMIT (Coordinated Medical Treatment of Opioid Use Disorder and Infectious Disease) is a National Center For Advancing Translational Science (NCATS)- funded (U01 TR002763) multi-site randomized controlled trial of adult patients hospitalized with opioid use disorder and associated infections comparing integrated treatment of long-acting buprenorphine (LAB) with infectious disease care (ID/LAB) compared to treatment as usual (TAU). Adult patients ($N = 200$) hospitalized with severe bacterial or viral infections (e.g., complications of HCV, HIV) related to OUD are recruited upon admission to hospital and randomized 1:1 to one of two models of care: 1) Infectious Disease management of OUD with Long-Acting injectable buprenorphine (ID/LAB), vs. 2) Treatment as Usual (TAU). ID/LAB is the new model in which OUD is managed by Infectious Disease (ID) specialists and/or Hospitalists concurrent with management of the infectious diseases, using long-acting injectable buprenorphine followed by referral to community-based care for long-term management with buprenorphine or other MOUD. TAU is designed to represent the current standard of care in most U.S. hospitals, in which typically buprenorphine treatment is used to manage opioid withdrawal symptoms with referral to community-based addiction treatment at time of discharge. The primary outcome measure is the proportion of patients enrolled in effective medication treatment for OUD (buprenorphine, methadone, or injection naltrexone) at 3 months (12 weeks) after randomization. Study sites are three hospitals serving geographically diverse, mixed urban and rural communities across the Eastern U.S.: (1) Yale New Haven Hospital (YNHH) in New Haven, CT; (2) Prisma Health System in Greenville, SC; and (3) Penn State Hershey Medical Center, in Hershey, PA. The study was funded in July of 2019, recruitment began in August of 2020 and is scheduled to end in the Summer of 2022. The study design is summarized in Fig. 1.

2.2. Ethical oversight

Institutional Review Board (IRB) oversight was centralized through the single IRB (sIRB) mechanism at the Medical University of South Carolina (MUSC). As per SMART IRB guidelines, Reliance Agreements were made between each recruiting site IRB and the MUSC IRB. These agreements accommodated regulatory and ethical language required by both the sIRB and each local site. The study is registered on clinicaltrials.gov (NCT04180020) and is a recipient of an FDA-approved IND as of May 29, 2020. An IND was obtained in lieu of REMS certification at the request of the pharmaceutical company providing Sublocade® and addresses the accelerated sublingual buprenorphine induction protocol (*see below*) for these hospitalized patients.

2.3. Research goals

This study tests the hypothesis of an integrated model of care for infectious disease and OUD treatment to synergize care and improve outcomes in persons hospitalized with both OUD and infections. The primary outcome is the binary receipt of any form of MOUD (e.g., buprenorphine, including sublingual and injectable formulations; methadone; extended-release naltrexone) at the end of the 12-week intervention analysis time point. Other secondary outcomes include: OUD outcomes (retention on MOUD treatment; number of days using opioids and injecting drugs; confirmed opioid abstinence via self-report or negative urine toxicology) and infectious disease management outcomes (completion of antimicrobial treatment course; re-hospitalization for infection).

2.4. Sample size and power calculations

Published data on buprenorphine initiation in the acute care setting [26,27] suggest a post-discharge retention of approximately 70%. A key study performed in the emergency room setting [26] contained an arm similar to TAU with post-emergency department discharge retention on buprenorphine of 45% at 1-month post randomization. Given that the expected patient population to be recruited in this study will be those who are the most severely ill with OUD and hospitalized with infections, we conservatively estimated a 12-week retention rate to be 60% in the ID/LAB arm and 40% in the TAU arm. Sample size of 200 study participants randomized to 1:1 will allow the detection of a difference of 19.7% (40% vs 59.7%) significant with power of 80% and on level of significance 5%. Such difference is considered clinically meaningful.

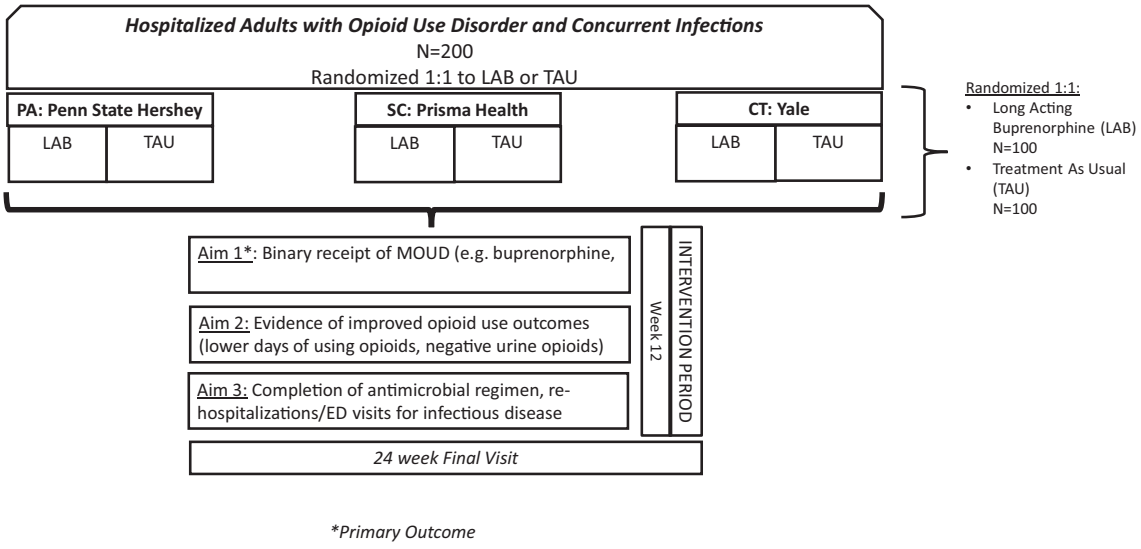

Fig. 1. Study design.

3. Study procedures

3.1. Recruitment and screening

Recruitment began in August 2020 and will continue until mid-2022. All recruitment occurs in the inpatient hospital setting with referrals coming from inpatient providers from hospitalists, infectious diseases, addiction medicine, or the Emergency Department. A HIPAA waiver was obtained to allow for review of the electronic medical record for eligible participants.

Inclusion criteria are as follows:

1. Adult (age 18-65) volunteers able to provide written informed consent in English or Spanish; 2. Current hospitalization with a bacterial, fungal or viral (HIV/HCV/HBV) infection including but not exclusively: bacteremia, fungemia, osteomyelitis, endophthalmitis, septic thrombophlebitis, infected pseudoaneurysm, pneumonia, endocarditis, skin/soft tissue infection (SSTI), or septic arthritis; 3. Current moderate-to-severe OUD (Diagnostic Statistical Manual-5th Edition (DSM-5) [28]); 4. Willingness to accept assignment to either ID/LAB or TAU, and to participate in research follow-up visits. Addiction-related viral infections are candidates for enrollment if treatment for the infection is warranted and can be started in the inpatient or outpatient setting. For HIV, participants are required to be virally unsuppressed (Viral Load >200 copies/ mL) and either out of care or not adherent to their antiretroviral regimen.

Exclusion criteria are as follows:

1. Severe medical or psychiatric disability making participation unsafe (e.g. imminent suicide risk); 2. Pregnancy, planning conception, or breast-feeding for female participants; 3. Allergy, hypersensitivity or medical contraindication to buprenorphine; 4. Moderate-severe liver impairment in the judgment of the study investigator; 5. Preexisting enrollment on methadone or sublingual buprenorphine (SL-B) maintenance for past 30 days prior to hospitalization AND intending to remain on methadone or buprenorphine maintenance upon discharge (patients successfully maintained on MOUD are not eligible for the study); 6. Inability or unwillingness of subject to give informed consent.

In allowing for a broad array of infectious syndromes, the investigators aimed to maximize inclusion and generalizability for this study. While this approach comes with the tradeoff of limiting sample size and power for any given included infection, it supports the goal of providing a real world implementation analysis in line with other pragmatic trials in MOUD/ OUD and Infectious Diseases [29,30].

Participants who become incarcerated are not disenrolled as this is an intention-to-treat study, but assessments may be missed unless they can be performed via IRB approved remote processes. Study sites are not able to uniformly bring study drug into the Department of Corrections (DoC). If a participant is incarcerated after enrollment in the LAB arm, all efforts will be made to continue with follow up and communicate with DoC providers for continued MOUD receipt (if LAB not available, SL buprenorphine may be recommended).

3.2. Eligibility process, informed consent and enrollment

Inpatient referrals are pre-screened by study clinicians for tentative eligibility and, if appropriate, a research associate is deployed to discuss the study with the patient in the hospital and conduct the consent process and eligibility procedures. Patient willingness to accept randomization between study arms (LAB/Sublocade® versus TAU) for their OUD is assessed along with their interest/ability to participate in research visits for a total of 6 months.

After verbal and written consent has been obtained, patients are enrolled and randomized 1:1 to ID/LAB or TAU within 7 days of consent. If randomized to receive Sublocade ®, the timing of the initial injection takes into consideration anticipated barriers, such as upcoming surgery or temporary initiation on methadone by the primary team for withdrawal treatment requiring transition to buprenorphine.

4. Covariate and outcome measures

4.1. Screening and intervention measures

Screening and intervention measures to assess eligibility criteria are listed in Table 1 and described below. Upon obtaining consent, enrollment and baseline study procedures are conducted followed by randomization, with established study follow-up continuing at designated intervals for 6 months. Refer to Table 1 for the comprehensive study measures timeline.

4.1.1. Demographics, drug use and treatment history

This brief assessment records basic demographics such as race/ ethnicity, gender, and housing status. It also includes drug use and treatment history such as age at onset and current use of opioids and

Table 1
Study visit measures and schedule.

Study procedures	Screening process		Study entry	Week 1	Study Participation With Assigned Treatment				
	Pre-screening	Screening	Baseline/ randomization/ induction		Discharge	Week 4	Week 8	Week 12	Week 24
Intervention (LAB)			X			X	X		
Visit number		Visit 0	Visit 1	Vis2		Vis3	Vis4	Vis5	Vis 6
Eligibility									
Informed consent		X							
Screener		X							
Laboratory tests/diagnostic procedures									
Urine pregnancy test		X				X	X	X	X
Rapid HCV (confirmatory VL if applicable)			X					X	
Rapid HIV (confirmatory test if applicable)			X					X	
Urine toxicology			X			X	X	X	X
BMP (SOC)			X					X	
CBC (SOC)			X					X	
INR (SOC)			X						
LFTs (SOC)			X					X	
Hepatitis B Testing (DNA PCR if applicable)			X						
HIV VL (if HIV AB+)			X					X	
CD4+ Count (if HIV+)			X					X	
HCV VL (if HCV AB+)			X					X	
Interviews/questionnaires									
Demographics form			X						
MINI (SUD, DSM-5 d/o)			X						
AUDIT			X						
ASRS (for ADHD)			X						
WHOQOL-Bref			X			X	X	X	X
PHQ-9			X			X	X	X	X
PCL5 (PTSD)			X						X
Modified PEG Pain Scale			X			X	X	X	X
Sexual & IDU Risk Behaviors			X			X	X	X	X
Criminal Justice Questionnaire			X			X	X	X	X
Interpersonal Violence			X			X	X	X	X
Timeline Followback			X			X	X	X	X
Covid-19 Questionnaire			X			X	X	X	X
Clinical									
Medications			X	X		X	X	X	X
ID Questionnaire			X		X	X	X	X	X
Substance Use Treatment (SUTx) Form			X			X	X	X	X
					X				
COWS			X	X		X	X	X	X
Elixhauser Comorbidity Index			X						
Modified Systematic Assessment for Treatment Emergent Events (SAFTEE) with sedation/overdose information				X		X	X	X	X
Ramsay Sedation Scale			X	X		X	X	X	X
Implementation Qualitative Interview								X	
Compensation[a] (Med Management up to $90)			$50			$25	$25	$50	$50

LAB = Long Acting buprenorphine; SOC=Standard of Care; LFTS = liver function tests; VL = Viral load; SUD=Substance Use Disorder; ADHD = Attention Deficit Hyperactivity Disorder; PTSD=Post Traumatic Stress Disorder; PEG = Pain, Enjoyment of Life and General Activity; IDU=Injection Drug Use; COWS = Clinical Opiate Withdrawal Scale.

[a] Non-study visit MM visits are compensated at $5 a session.

other drugs/alcohol, history of overdose, history of substance related hospitalization, and past episodes of treatment for substance use disorders (SUD) including MOUD history. The Locator Form collects patient-related contact information to maximize retention.

4.1.2. Opioid and other substance use

The Clinical Opiate Withdrawal Scale (COWS) [31] is an 11-item scale used in both inpatient and outpatient settings to reproducibly rate common signs and symptoms of opioid withdrawal and monitor these symptoms over time. The Ramsay Sedation Scale [32] is a clinical assessment that grades a participant's level of sedation from 1 to 6 and is useful in assessing for excessive opioid agonist symptoms. Two additional questions assess intensity and number of days of opioid craving using a 10-point Likert scale. The Timeline Follow-Back (TLFB) [33,34] assesses self-reported alcohol and other drug use including opioid use, route of use and form of drug for the 30 days before baseline, and for each day over the follow up period as shown in Table 1. The Mini-International Neuropsychiatric Interview [35] (MINI) DSM-5 version 7.0.2 is utilized to establish a current moderate to severe OUD diagnosis and assesses for other co-morbid DSM-5 SUDs and major psychiatric disorders at baseline only. The Alcohol Use Disorder Identification Test [36] (AUDIT) assesses for presence and severity of alcohol use disorder at baseline only.

4.1.3. Mental health, social, and quality of life

The Patient Health Questionnaire (PHQ-9) [37,38] assesses major depression and generalized anxiety disorder at baseline. The PTSD Check List-5 (PCL5) for Post-traumatic Stress Disorder (PTSD) [39] is a 5-question assessment that evaluates for presence and severity of PTSD symptoms, common in this population affected by OUD and can affect

retention on MOUD. The Adult ADHD Self Report Scale (ASRS) for Attention Deficit Disorder (ADHD) symptoms [40] is an 18-question assessment for presence and severity of ADHD symptoms by self-report and is utilized in this study as ADHD is also common in persons with OUD and may affect retention on MOUD. The WHOQOL-Bref [41] is a well validated and widely used scale for persons with SUDs that measures the quality of social and occupational functioning as well as other domains. A Criminal Justice Questionnaire collects information on probation/parole status, and the Interpersonal Violence (IPV) asks about current and past relationships to assess history and current experiences with interpersonal violence. This is derived from the existing Partner Violence Screen (PVS) [42] and the Women Abuse Screening Tool (WAST) [42].

4.1.4. Medical and safety

There are two trial specific assessments that were created to capture infectious and substance use treatment outcomes as shown in the Appendix. The Infectious Disease Questionnaire (IDQ) is a study specific form that documents the type of infection and recommended treatment at baseline and the completion of antimicrobial therapy and re-hospitalization for infection at follow-up. The initial evaluation collects relevant infection and medical details such as infection site, organism, and stage. Information on follow-up is collected on alteration of treatment plan, infection-related adverse events and intervening hospitalizations. The Substance Use Treatment (SUTx) Form is another study specific questionnaire that documents the details of MOUD and substance use treatment history in the intervention and TAU arms at baseline and in follow-up visits. The Elixhauser Comorbidity Index [43] is a validated scoring index for predicting mortality based on patient comorbidity and is performed via chart review. The Modified (Pain, Enjoyment of Life and General Activity Scale) PEG Scale is adapted from the PEG Pain Scale [44] which is used to measure pain over time. Two questions have been added to the initial assessment to measure pain at time of interview and withdrawal-related pain. The HIV Risk Behavior tool (developed by author S.S.) is used to assess sexual risk behaviors and sharing of IDU-related equipment [45]. As of July 2020, a COVID-19 Questionnaire, also shown in the Appendix, was added to the protocol to assess: 1) testing for COVID-19, 2) diagnosis of COVID-19, 3) changes in substance use and 4) changes in infection self-management by participants due to the COVID-19 pandemic.

4.1.5. Laboratory analyses

A rapid test for HIV [46] or HIV P24ag/antibody serum test is performed on all consented participants for whom HIV status is not known at time of baseline interview followed by confirmatory blood testing if positive. In addition, rapid HCV testing or serum HCV Antibody with reflex HCV Viral load testing will also be carried out for those with unknown HCV status. Positive rapid results will be confirmed though confirmatory blood tests (HCV AB, HCV viral load). Other labs include hepatitis serum surface antigen (HBSAg), surface antibody (HBSAb), core antibody (HBcAb), and quantitative HBV DNA PCR if surface antigen is positive. Basic metabolic panels (BMP), complete blood counts (CBC), and liver function tests (LFTs) are recorded at baseline and week 12 as per standard clinical care. For persons of childbearing potential, a urine pregnancy test will be done at baseline prior to urine drug testing. If the test is positive, a confirmatory pregnancy test will be ordered. Participants who are pregnant at baseline or become pregnant are ineligible to participate in the study. Urine pregnancy tests will also be done at each follow-up visit. Lastly, urine drug toxicology screens (13 drug panel: amphetamines, buprenorphine, benzodiazepines, cocaine, methamphetamine, ecstasy, methadone, opioids, oxycodone, cannabis, alcohol, fentanyl, tramadol) are performed at each study visit.

4.2. Process measures

4.2.1. Qualitative interviews

In addition to outcome measures, qualitative interviews are conducted at a time point between the week 12 and week 24 study visits with the first five patients at each study site assigned to the ID/LAB model to elicit personal accounts of their experience with the service, its acceptability, and suggestions for improvement. The physicians and nurse care managers delivering ID/LAB services and standardized counseling at each site are also interviewed similarly after the 12 week time point but before the 24 week study visit after starting enrollment to obtain feedback about feasibility, acceptability, barriers, and facilitators within their practices and suggestions for improving implementation. An interview guide was developed in consultation with clinical teams, and incorporated standard implementation outcomes [47]. The interviews are recorded and transcribed. Using Atlas.ti© software and a coding framework, designated research staff personnel systematically code transcripts of the interviews to identify themes that are discussed at the weekly-convened study team conference call with the MPIs, Site PIs, and local site study coordinators. The implementation assessment will be used to collect data from patients and providers in a more holistic fashion to further understand the utility of the ID/LAB model and improve generalizability. These descriptive implementation data will help identify facilitators and barriers to implementation of the model and will inform development of a brief guideline to support dissemination of the model beyond the study. Once completed, the guideline will be distributed to stakeholders after the study for those institutions to use to refine their clinical processes.

5. Randomization and dispensing

Participants are randomized to one of the two study arms (ID/LAB vs TAU) using fixed permuted blocks of 4 and stratified by study site. The randomization was designed by the study statistician and integrated into the data system by the study data manager, who otherwise have no direct contact with study staff evaluating and managing the participants, and study staff have no access to the random sequence of treatment group assignments. Once a patient has consented and has been determined to be eligible, the study site coordinator enters the participant into the data system, registers the participant, obtains a unique study ID number, and the randomized group assignment is generated by the system (ID/LAB or TAU). Treatment under the assigned study arm then begins after randomization assignment.

Sublocade® was provided without financial cost by the manufacturer Indivior Inc. The study drug is managed by Investigational Drug Pharmacies at each site to ensure maximal drug management and accountability, including controlled substances disposition. This trial is non-blinded with no placebo drug utilization.

6. Intervention

6.1. Study procedures

6.1.1. Pre-discharge

After enrollment, baseline interview data is collected and then entered directly into the study database through a secure online platform. Study assessments are performed by research associates (RAs) and clinical researchers (CRs) (see Table 1). If not already available through the electronic health record, HIV, HCV and urine drug screen testing is performed. For those who had newly confirmed or previously known HIV and/or active HCV, viral load testing is obtained. Specific laboratory data is collected through standard clinical care.

6.1.2. Infectious disease and long-acting buprenorphine intervention

For those in the *ID/LAB arm,* it is expected that Sublocade® will be administered within 7 days of randomization as described above.

Sublingual buprenorphine induction can be performed by any of the clinical teams (infectious disease, hospitalist, or addiction medicine consultants) with the assistance of DEA X-waivered research clinicians if necessary. Flexibility is afforded as to the buprenorphine induction protocol that is used, however a minimum of 16 mg of sublingual buprenorphine needs to be administered for at least 2 days with a reduction in opioid withdrawal symptoms based on a COWS [31] score of less than 5 and no evidence of over sedation or opioid agonist effects [32] prior to Sublocade® administration. In addition, a Clinical Readiness Checklist (see Appendix) was designed to ensure medical appropriateness and safety prior to study drug receipt. An FDA IND was obtained to obviate the need for Risk Evaluation and Mitigation Strategy (REMS) pharmacy certification; additionally, FDA clearance was granted for Sublocade® to be administered earlier than 7 days of maintenance on sublingual buprenorphine if felt to be clinically warranted and appropriate for this study. This is supported by published data [48] with the rationale that induction onto Sublocade® could be rapid enough to not prolong the patient's hospitalization while still maintaining patient safety. The pivotal trial leading to FDA approval of Sublocade®, conducted in an outpatient setting, required seven days of at least 8 mg of SL buprenorphine prior to the first dose of Sublocade®. This is a cautious approach to ensure buprenorphine is tolerated prior to administering the LAB formulation. However, recent evidence suggests Sublocade® can be administered after a patient tolerates one or two days of sublingual buprenorphine [48]. In the inpatient setting in patients with moderate to severe OUD, the accelerated induction addresses the urgency to administer long-acting buprenorphine, particularly for those patients who may be discharged imminently. There is no strict preclusion to Sublocade® being administered as an outpatient as long as all other aforementioned criteria are met.

Once the Sublocade® is administered, the COWS [31] and Ramsay Sedation [32] assessments continue to be performed at 30-min intervals for two hours by study team clinical researchers to assess for precipitated withdrawal or over-sedation. Daily COWS and Ramsay assessments are performed either until discharge or for 7 days and at each scheduled follow-up clinical research visit. Participants may receive SL buprenorphine in addition to their Sublocade® in both the inpatient and outpatient setting if felt to be clinically warranted.

The model of integration between Addiction and Infectious Disease care in the ID/LAB arm begins in the hospital at randomization. The ID and hospitalist inpatient teams are empowered to initiate SL buprenorphine in anticipation of Sublocade® receipt. There is additionally a research staff Nurse Care Manager who provides ongoing structured counseling, discharge planning, and overdose education/naloxone distribution to participants in both study arms (see '*Nurse Care Manager Model*' section below). This provides continuity through the discharge process and into the outpatient realm. In the outpatient setting, a significant proportion of patients will have clinically indicated Infectious Diseases follow-up which allows for further unique integrated care to occur in the ID/LAB arm – participants can get their Sublocade® injections and their Infectious Disease follow-up during the same visit. Once a clinical relationship has been established, these ID providers can continue MOUD prescribing as needed and in some cases even beyond the study participation if long term clinical follow-up occurs. In the case of shorter follow-up, the process of linking participants to outpatient MOUD providers begins almost immediately upon enrollment to ensure a smooth and durable transition to care continuity. As Sublocade® is FDA approved and commercially available, linkage to community Sublocade® providers is facilitated for those who prefer to stay on the medication post study.

6.1.3. Treatment as usual (TAU)

The *TAU arm* is designed to reflect current usual care at the participating hospitals. The approach to management of OUD in medical hospital settings varies based on regional and institutional capability and has evolved since the study was initially proposed. There are differences based on hospital settings throughout the country in what the standard of care is regarding OUD treatment and medical withdrawal treatment with opioid agonist therapy (buprenorphine or methadone), transition to maintenance therapy with one of the forms of FDA-approved MOUD (e.g., methadone, sublingual and long-acting buprenorphine, or extended-release naltrexone) and/or referral to MOUD treatment or other services on discharge. At a minimum for this study, participants in both arms including the TAU arm receive: 1) a formal diagnosis of DSM-5 moderate to severe OUD; 2) education regarding the diagnosis of OUD; 3) verbal and written educational information about the different FDA-approved forms of MOUD and where they can receive them if interested; 4) opioid overdose education with recommendation to team to provide prescription for naloxone distribution at discharge; and 5) a recommendation to the primary Medicine/Infectious Diseases team for initiation of MOUD and naloxone distribution (Informational materials included in Appendix). There are no barriers to the clinical care provided in the TAU arm – Addiction Medicine consultation, if felt to be warranted by the team, is acceptable. At the PRISMA site, there was no Addiction Medicine service at the of study startup and inpatient initiation of MOUD is uncommon. At the Penn State Hershey site, there is a burgeoning Addiction Medicine consultation service while at the Yale site the Addiction Medicine consult service is robust and inpatient MOUD initiation is common. Linkage to obtain commercially available Sublocade® is not prohibited.

6.1.4. Nurse care manager model

Participants in both study arms receive standardized counseling in the context of a *Nurse Care Manager model*. The Nurse Care Manager model utilizes nurses or Physician Assistants to evaluate and follow patients with OUD in collaboration with physicians – while the initial model utilized nurses, for the purposes of this study any research clinician can be trained to conduct this counseling [49,50]. If a licensed clinician is not available; other members of the research team can be trained to conduct the standardized counseling with a clinician available as resource personnel. The nurse care manager (NCM) follows the participants clinically from screening and evaluation onward and communicates with them twice a week while inpatient and weekly until linkage to outpatient substance use referral is secured. The standardized counseling uses the Medical Management (MM) which is a brief 15-min intervention that has been employed widely in alcohol and opioid medication trials that advocates for abstinence and recommends adherence to medication treatment [51,52]. A structured interview and progress note form is utilized when conducting the MM. In the ID/LAB arm, MM for this study focuses on the following: adherence to medication treatment (both for the infections and the LAB for OUD); evaluation of potential medication side effects (including adverse events); abstinence from illicit opioids and other drugs and alcohol (accepting minimal use if abstinence is not the patient's goal); and engagement in optional community-based counseling and treatment resources. The NCM works with the patients to transition their OUD care from the ID/LAB team during hospitalization to a community-based treatment program for ongoing medication treatment. In the TAU arm, the NCM works with the primary team and participants on a schedule similar to the ID/LAB arm, providing additional counseling on abstinence and discussing the importance of engagement in medication treatment for OUD which may include MOUD treatment based on the provider's choice and institution's policies.

6.1.5. Discharge

Time of discharge is a floating time point in the study assessment schedule (see Table 1). This was designed to accommodate the large variation in the hospital lengths of stay for participants (e.g., soon after enrollment versus sustained hospitalization through the week 12 time point). When discharge is anticipated, the study research team collaborates with hospital care management to ensure linkage to care has been established for outpatient substance use management. In addition, in the

ID/LAB arm the Nurse Care Manager will aid in discharge planning. Recommendation is given to the primary medical teams for all participants to be discharged with naloxone or a prescription for naloxone if being discharged to home. The assessments performed at the discharge time point retrospectively assess the Infectious Disease and Substance use management that occurred during the hospitalization.

6.1.6. Follow-up research visits

Follow-up research visits occur at the time intervals listed on Table 1 either at research offices or via coordination through clinical follow-up visits. Assistance is provided for all participants for linkage to all clinically necessary outpatient providers such as substance use treatment and, if needed, outpatient infectious disease treatment. Urine drug screens and, when applicable, urine pregnancy testing, is performed at each follow-up visit. MM is conducted with all study participants regardless of study arm and occurs twice a week while admitted, then once a week after patients are discharged from the hospital either in person or over the telephone.

At the 12-week visit additional laboratory data are obtained including repeat testing for HCV and HIV in addition to urine drug screening and urine pregnancy testing, if applicable. Specific laboratory analyses that are performed in the context of regular clinical care, including liver function tests, are also documented.

6.1.7. Injection procedures

For those participants assigned to the ID/LAB treatment intervention arm, study drug (Sublocade®) (LAB) administration is linked when possible to outpatient clinical visits for substance use or infectious disease management. Participants in the ID/LAB arm who have not linked or engaged with continued outpatient management post-discharge will be seen by the research team to receive the study drug for their first three doses. Prior to Sublocade® injection, the dose is determined by the local site investigator and rotation of administration site (e.g., abdominal quadrant) will be assured. Sublocade® has two doses, 300 mg and 100 mg. For this study, the 300 mg dose was chosen to be used at all time points, however discretion is given to the site PI to use the 100 mg dose if there are potential for opioid agonist side effects such as with the coadministration of antimicrobials that might prolong the level of Sublocade®. A brief physical exam is performed to assess for any abdominal pathology that would preclude drug administration and a clinical safety assessment form is completed. The study drug is administered every 28 days with a window allowing for dosing 2 days earlier or up to 14 days after the scheduled date, as per the package insert. As the study drug in COMMIT is not blinded, participants are aware of study arm allocation and no placebo injections are given.

7. Payments

Participants are compensated for donating their time to clinical research and not for receiving study medication as shown in Table 1. All payments are made in cash or gift card equivalent per site discretion. The study visits are compensated at a value of $50 for the baseline visit, week 12, and week 24 visits. Weeks 4 and 8 are compensated at $25. The non-study visit weekly Medical Management check-ins performed by the Nurse Care Managers are apportioned $5 per call with an opportunity for payment for up to 18 check-ins. Cash value of the total study payments are $290.

8. Specific safety protocols

All participants are screened prior to enrollment by a clinical researcher and the local site investigator if needed to ensure appropriateness for the study. Those with severe medical or psychiatric comorbidity precluding safe participation are excluded. Buprenorphine products are not recommended for use in severe hepatic impairment – prior to enrollment all available clinical data is reviewed to assess for severe liver disease such as significant transaminitis or advanced cirrhosis. If any additional information is needed to make the determination, such as outstanding lab analysis, these tests are requested through the primary hospital team.

As all participants in this study are enrolled while in the inpatient setting, many receive long-term antimicrobial therapy that is paired with laboratory monitoring. Liver function tests, complete blood counts, and metabolic panel data ordered via standard of care are documented and monitored by the research study staff. Participants are assessed at the Week 4, 8 and 12 time points by Clinical Research staff as well as for focused physical examination and to assess for any clinical changes that may merit further laboratory testing.

For those in the ID/LAB arm, a clinical checklist is utilized to ensure readiness for Sublocade® administration prior to injection. Safety wallet cards are provided to all participants that include study arm allocation which can be given to healthcare providers to inform of their study participation and medications.

If a participant develops severe hepatic disease while receiving Sublocade®, the etiology will be assessed by the local site investigator and a decision will made regarding discontinuation of the study medication. Those with uncontrolled SUD in the study are referred to higher-level substance use care if felt to be warranted.

Adverse events are reported on a modified version of the validated Systemic Assessment for Treatment of Emergent Events (SAFTEE) form [53,54] by the clinician nurse/ researcher at least every month for the first 3 months of the study as well as three months after the last injection as shown in Table 1. Adverse events that occur between scheduled assessments are reported using the same form. All adverse event definitions are in keeping with standard FDA designations of non-serious and serious adverse events.

9. Analytic plan

Below are brief descriptions of the planned analyses categorized by variable.

9.1. Substance use outcomes

The *primary outcome* is a binary indicator of whether a patient is enrolled in and receiving effective MOUD (buprenorphine, methadone, or injection naltrexone) at 12 weeks (3 months) after randomization. Receipt of MOUD is verified by either documented medical records via release of information from the treatment program, or if the treatment program does not respond, prescription drug monitoring report or electronic medical record (EMR). The authors considered as an alternative a primary outcome measure reflecting opioid use (e.g., opioid free weeks or abstinence at end of study as often favored by the FDA, or opioid relapse as used in the in the X:BOT trial [55] and in an extended-release naltrexone vs. TAU criminal justice trial) [56]. However, the primary goal of the ID/LAB model of care being tested is to secure transition onto MOUD. Substantial evidence from longitudinal studies suggests that being on effective MOUD is essential to maintaining abstinence, and risk of relapse to opioid use is high if buprenorphine or other medication treatment is discontinued [57,58].A binary indicator, while it sacrifices some information, has the virtue of having a straightforward clinical meaning, particularly in this trial where the goal is to determine whether the ID/LAB model, where the medical team directly manages OUD with LAB during hospitalization, increases the likelihood of transitioning successfully to medication maintenance treatment in the community. Participants who are on oral medications (SL buprenorphine, methadone) are considered to be retained on MOUD if their last documented dose (via medical record or, if not available, prescription) occurred within 14 days of the week 12 follow-up visit and assessment. Participants maintained on depot formulations (LAB, extended release naltrexone) are considered to be retained on MOUD if their last documented dose occurred with 42 days (28 days plus 14 day

window). This 14 day "window" period was selected since this is the date range provided in the Sublocade® package insert for continued efficacy beyond the expected 28- day follow-up injection period – for uniformity this window period has been carried over for all MOUD forms.

Days using opioids and days injecting drugs per 28 days prior to each major assessment point and urine toxicology confirmed abstinence are *secondary outcomes*. The opioid outcomes are likely to be associated with continued MOUD treatment and will be key secondary outcomes.

9.2. Infectious disease outcomes

While not a primary outcome, a major aim of this study protocol is to test whether the integrated ID/LAB model of care results in higher rates of antimicrobial treatment for their infectious disease and decreased re-hospitalizations/ED visits. Antimicrobial treatment completion is assessed as a binary variable based on adherence to the Infectious Disease/hospitalist directed treatment plan for a given index infection. Treatment adherence and missed doses are determined through Electronic Health Record review. Treatment success is defined as completion of prescribed antimicrobial therapy on a given date without missed doses – for those who have formalized changes in their antimicrobial treatment plan for medically indicated reasons (e.g., drug reaction), this is construed as an alteration in the treatment plan and not a treatment failure per se. At the week 12 time point, the electronic health record and any other relevant chart documentation are reviewed by the study Infectious Disease physicians to assess likelihood of treatment failure (definite, possible, or none).

9.3. Additional outcomes

In addition to substance use and infectious disease related outcomes, additional exploratory variables are being assessed: HCV cure, HIV viral suppression, social functioning and quality of life; pain assessment; HIV risk behaviors (sexual and injection drug use related); treatment satisfaction and adverse event reporting.

9.4. Statistical analyses

All analyses will be performed on the Intent-to-treat (ITT) sample, and all tests will be performed at a two-sided significance level of 5%. For the primary outcome, the effect of randomization to the ID/LAB arm compared to the TAU arm will be estimated using logistic regression with the binary outcome of enrollment (yes/no) modeled as a function of treatment condition (ID/LAB vs TAU), adjusted by site as a fixed effect, and covariates/moderators as listed above under 'Additional Variables'. The odds ratio of the treatment term and its confidence limits will estimate the treatment effect. Additionally, we will compute the modeled proportion for each combination of the categorical predictors and selected values of continuous predictors and present those to improve the interpretations of the results. For each of the secondary outcomes the effect of randomization to the ID/LAB arm compared to the TAU arm will be estimated with a generalized linear model with appropriate link function (log link function for continuous outcome following log-normal or negative binomial distribution, identity link function for continuous outcomes following normal distributions, or logit link function for binary outcomes). The models will consist of main effect of treatment assignment (ID/LAB vs TAU), adjusted by site as a fixed effect, and baseline score of the outcome as covariate where relevant. Longitudinal outcomes analyzed using longitudinal generalized mixed effect models with embedded autoregressive correlation structure (AR(1)) to account for within subject correlation over time, as well a random intercept accounting for between subject variability. In addition to site, covariates that are found to be related to the outcomes but not treatment assignments will be added to the models to improve the power for detecting significant differences between treatment assignments.

For the primary outcome and secondary outcomes related to treatment engagement, any patients lost to follow-up will be assumed to have not enrolled in treatment nor have completed the antimicrobial course. For the secondary outcomes related to substance use, missing data (patients who cannot be located) will assumed to be opioid positive (not abstinent), a typical assumption which is reasonable based on the high rate of relapse among patients with OUD who discontinue MOUD [58–61]. For other secondary outcomes, missing data will be treated as missing at random [62]. We will additionally perform sensitivity analysis for the secondary outcomes to examine the influence on the outcomes of dropout and missing data by performing several imputation methods, for instance imputing missing weeks as all abstinent or all non-abstinent.

10. Implementation issues

There have been several implementation issues that were overcome prior to and during the conduct of this study, summarized below.

10.1. Study drug procurement; FDA IND

On April 1, 2020, the research team was notified by the Indivior pharmaceutical company that to obtain the study drug (Sublocade®), either a Risk Evaluation and Mitigation Strategy (REMS) certification needed to be obtained by all research pharmacies or an Investigational New Drug (IND) in order to expedite disbursement of Sublocade®. The IND application was submitted to obviate the REMS need. Of note, Sublocade® was FDA approved in 2017 for use in persons with moderate to severe DSM-5 OUD who have been inducted onto a stable dose of sublingual buprenorphine of at least 8 mg for 7 continuous days. The pharmaceutical company and the researchers suggested that the IND pathway would allow expeditious study drug supply, so an IND application was prepared with support from the Yale Center for Clinical Investigation (YCCI) and submitted on April 28, 2020. Based on a request from the FDA, a minor protocol amendment was created due to the accelerated SL BUP induction to collect additional participant safety data in the immediate period post-administration of Sublocade® and for seven days afterwards. FDA approval was granted on May 29, 2020. Study drug was sent to the Investigational Drug Services at each site and was received by the Yale site on August 6, 2020, by Prisma Health Care on July 31, 2020 and by Penn State Hershey on October 27, 2020.

10.2. Covid-19 pandemic

The emergence of the SARS-CoV-2 respiratory virus and its subsequent global spread created a cataclysmic change in healthcare and clinical research structures around the world. On March 13, 2020 Yale University suspended non-COVID-19 related research activities to reduce viral spread. This policy was implemented prior to recruitment and study start-up but halted plans for impending study initiation. At Penn State Hershey and PRISMA-Greenville sites non-COVID-19 related research initiation/continuation was considered on a case-by-case basis. Institutional variation in practice was in part due to the significant regional differences in severity of U.S. COVID-19 spread. All research programs at Yale were required to create a COVID-19 mitigation plan to be assessed by institutional leadership prior to sanctioned recurrence of research activities. This mitigation plan was completed for this study and emphasized the following key concepts: physical distancing, personal protective equipment (PPE), symptom screening, de-densification of workspaces, contact tracing, and decontamination practices. The top priority was to ensure the safety of both participants and research staff members to prevent undue transmission of SARS-CoV-2. A particular challenge was the creation of mechanisms to safely obtain informed consent in the inpatient setting if in-person visitation was not feasible. FDA guidance on conduct of clinical trials during the pandemic was

published in March of 2020 [63] and later updated in September 2020 that provided the framework for these alterations, and a protocol for two-person telephone consent was designed using these guidelines. The option of remote telephone visits for interviews that could be conducted remotely was added. Plans approved by the IRB included not enrolling participants who were either suspected or confirmed to have COVID-19. For the portions of study visits that needed to be in-person, COVID-19 mitigation strategies were developed in line with Centers for Disease Control (CDC) guidance [64] that would accommodate the varying epidemiology and regulations of each clinical site in those who were discharged to the community as well. These included: 1) Addition of participant screening for active COVID-19 symptoms and referral to inpatient care when needed, 2) Procurement of COVID-19-compliant PPE (e.g.: N95 mask, face shield, gown, glove) for necessary clinical care for those who test positive for COVID-19, and 3) Universal precautions of masking and glove use during all participant interactions.

11. Summary

Medication treatment is recognized as the most effective treatment for OUD [65], and studies have shown that initiation of MOUD in hospital settings can improve OUD treatment outcomes [26,27]. Unfortunately, however, few persons are screened for OUD in hospital settings when admitted for infections or other medical comorbidities and few are offered maintenance MOUD to prevent opioid craving, manage opioid withdrawal symptoms or to reduce risk of relapse after discharge [66]. Without addressing patients' OUD, infectious disease management is undermined. The National Academies of Science, Engineering and Medicine (NASEM) [17,67], the Infectious Disease Society of America (IDSA) & HIV Medicine Association (HIVMA) [19], and National Institutes of Health (NIH) [68] have all called for improved integration of ID and OUD treatment to reduce the morbidity and mortality associated with these dueling epidemics [17]. To date, however, no study has evaluated the integration of MOUD with ID care for persons admitted to hospitals with OUD and infections. This study is the first to evaluate the use of an integrated model where OUD and infectious disease care are offered by the IDs/ hospitalist team using a long-acting formulation of buprenorphine to improve their OUD and Infectious disease outcomes.

Sustained retention on MOUD is key to ensuring patients do not relapse to opioids, overdose and die, as well as essential to ensuring patients can complete their antimicrobial therapy when admitted with concurrent infectious diseases. Relapse to opioids can interfere with the ability to complete extended courses of antimicrobial therapy for invasive infections like endocarditis (potentially 2–6 weeks), bone and joint infections (potentially up to 8 weeks or longer), hepatitis C (8–12 weeks) or HIV (chronic treatment), and leads to high morbidity and mortality. Buprenorphine remains the first line treatment for OUD and can be prescribed by physicians who receive an 8-h training (and advanced practice nurses and physician assistants who receive a 24-h training) in any medical care setting [13,69]. Of note, in the hospital setting buprenorphine ordering is exempt from waiver requirements per US Federal Law. Prior studies suggest a typical retention rate of SL buprenorphine of only 30–40% at 6 months [70]. Many clinicians, both within and outside of the addiction field, hesitate to prescribe buprenorphine in its current formulation because of concerns about the high risks of early drop out, relapse and potential for drug diversion [71].

Long-acting formulations of buprenorphine (LAB) represent a potential breakthrough in the treatment of OUD, potentially reducing the risk of treatment dropout and clinical relapse. Long-acting formulations of medications in general have been associated with better medication adherence when compared to their oral counterparts [72–75]. The injectable monthly formulation of buprenorphine (Sublocade®) has already been shown to be well tolerated and associated with 64–66% retention in treatment at 12 months as compared to only 34% on placebo [25,76]. Another long-acting injectable buprenorphine product, Brixadi® formerly CAM-2038, was found to be non-inferior to daily SL-buprenorphine on abstinence and superior to sublingual buprenorphine on several secondary opioid abstinence outcomes [24]. While these formulations have been tested in persons with moderate to severe OUD, those with concurrent infections have been excluded from evaluation and yet are the most in need of evaluation of whether a long-acting formulation of buprenorphine (LAB) can most benefit them.

This non-blinded randomized controlled trial has been designed to create an integrated model of care between ID/addiction that answers key endpoints and maintains external validity. Participants are randomized in a 1:1 fashion between the ID/LAB and TAU arm- the ID/LAB arm includes 3 months of subcutaneously administered Sublocade® free of charge, and the total period of observation per participant for both arms is 6 months. The challenge in the design of the TAU arm was in creating a study condition that acknowledged the reality of the limited OUD treatment that is common across healthcare while maintaining a minimum standard of care. In the initial conception of the study, TAU was described as "detoxification" and referral to outpatient treatment. Despite this being a common practice, the study leadership felt that current guideline recommendations are clear in their emphasis on maintenance MOUD as a cornerstone in OUD treatment [77]. Hence the TAU condition was altered to ensure that the study team conveyed to the primary medical team that the current recommendation is for initiation of MOUD with additional standardized information on MOUD choice provided to both the participant and to the team. In some settings the options for addiction management may even include Addiction Medicine consultation. It remains to be seen whether the MOUD prescription on discharge will be higher in the TAU arm than standard clinical practice. Despite this bias potentially favoring the null hypothesis, it was ethically important to the authors to create a control group that was patient centered and enforces guideline management as opposed to suboptimal clinical practice.

In addition to the anticipated challenges that have arisen in the course of early implementation of this trial, the COVID-19 pandemic added a new unanticipated layer of challenges to be overcome. The pandemic resulted in a delay of initiation of the study across all sites as well as new barriers to in-person research. However, our research team was able to adapt in the context of the circumstances and employ new practices to ensure mitigation of spread of the virus via remote consent processes and creation of a comprehensive COVID-19 mitigation plan. We believe these practices have ultimately made our trial more flexible and responsive to current and future research needs.

In this first study of integration of LAB for OUD with infectious disease management, we hypothesize that LAB, in this case Sublocade®, will be particularly advantageous for the population of patients hospitalized with OUD-related infections. This population is prone to non-adherence and relapse, particularly in rural or under-resourced areas where there are challenges and delays to securing follow-up treatment. The extent to which this new treatment (LAB) facilitates retention of hospitalized patients on long term MOUD post-discharge, decreases opioid use, and retains people on their antimicrobial treatment for related infectious diseases, has not been evaluated in any long-term effectiveness trial. The rigorous evaluation of LAB compared with current standard of care for hospitalized patients with infections related to OUD that has been described above will provide crucial data to guide the response to the current opioid epidemic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2021.106394.

References

[1] L. Scholl, P. Seth, M. Kariisa, N. Wilson, G. Baldwin, Drug and opioid-involved overdose deaths - United States, 2013-2017, MMWR Morb. Mortal. Wkly Rep. 67 (5152) (2018) 1419–1427.
[2] L. Sherry, J.X. Murphy, D. Kenneth, Elizabeth Arias Kochanek, Mortality in the United States, 2018, NCHS, 2018.
[3] A.J. Schranz, A. Fleischauer, V.H. Chu, L.-T. Wu, D.L. Rosen, Trends in drug use–associated infective endocarditis and heart valve surgery, 2007 to 2017: a study of statewide discharge data drug use–associated infective endocarditis and valve surgery, Ann. Intern. Med. 170 (1) (2019) 31–40.
[4] A.Y. Zhang, S. Shrum, S. Williams, et al., The changing epidemiology of Candidemia in the United States: injection drug use as an increasingly common risk factor—active surveillance in selected sites, United States, 2014–2017, Clin. Infect. Dis. 71 (7) (2019) 1732–1737.
[5] P.J. Peters, P. Pontones, K.W. Hoover, et al., HIV infection linked to injection use of oxymorphone in Indiana, 2014–2015, N. Engl. J. Med. 375 (3) (2016) 229–239.
[6] J.E. Zibbell, A.K. Asher, R.C. Patel, et al., Increases in acute hepatitis C virus infection related to a growing opioid epidemic and associated injection drug use, United States, 2004 to 2014, Am. J. Public Health 108 (2) (2017) 175–181.
[7] M.V. Ronan, S.J. Herzig, Hospitalizations related to opioid abuse/dependence and associated serious infections increased sharply, 2002-12, Health Affairs (Project Hope) 35 (5) (2016) 832–837.
[8] E.V. Nunes, M. Gordon, P.D. Friedmann, et al., Relapse to opioid use disorder after inpatient treatment: protective effect of injection naltrexone, J. Subst. Abus. Treat. 85 (2018) 49–55.
[9] I.A. Binswanger, M.F. Stern, R.A. Deyo, et al., Release from prison—a high risk of death for former inmates, N. Engl. J. Med. 356 (2) (2007) 157–165.
[10] E. Ravndal, E.J. Amundsen, Mortality among drug users after discharge from inpatient treatment: an 8-year prospective study, Drug Alcohol Depend. 108 (1–2) (2010) 65–69.
[11] D.P. Serota, J.A. Barocas, S.A. Springer, Infectious complications of addiction: a call for a new subspecialty within infectious diseases, Clin. Infect. Dis. 70 (5) (2020 Feb 14) 968–972.
[12] L.R. Marks, S.Y. Liang, D. Muthulingam, et al., Evaluation of partial oral antibiotic treatment for persons who inject drugs and are hospitalized with invasive infections, Clin. Infect. Dis. 71 (10) (2020) e650–e656.
[13] R.P. Mattick, C. Breen, J. Kimber, M. Davoli, Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence, Cochrane Database Syst. Rev. (2) (2014), Cd002207.
[14] R.P. Mattick, C. Breen, J. Kimber, M. Davoli, Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence, Cochrane Database Syst. Rev. (3) (2009), Cd002209.
[15] E. Krupitsky, E.V. Nunes, W. Ling, A. Illeperuma, D.R. Gastfriend, B.L. Silverman, Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial, Lancet (London, England) 377 (9776) (2011) 1506–1513.
[16] K.J. Li, D.L. Smedberg, L.E. DeLisi, A retrospective 4-year outcome study of veterans admitted to an acute inpatient detoxification unit for opioid use disorder, Am. J. Addict. 28 (4) (2019) 318–323.
[17] S.A. Springer, A.P. Merluzzi, C. del Rio, Integrating responses to the opioid use disorder and infectious disease epidemics: a report from the National Academies of Sciences, Engineering, and Medicine, Jama 324 (1) (2020) 37–38.
[18] S.A. Springer, C. del Rio, Addressing the intersection of infectious disease epidemics and opioid and substance use epidemics, Infect. Dis. Clin. 34 (3) (2020) xiii–xiv.
[19] S.A. Springer, J.A. Barocas, A. Wurcel, et al., Federal and state action needed to end the infectious complications of illicit drug use in the United States: IDSA and HIVMA's advocacy agenda, J. Infect. Dis. 222 (Supplement_5) (2020) S230–S238.
[20] S.A. Springer, A. Di Paola, M.M. Azar, et al., Extended-release naltrexone improves viral suppression among incarcerated persons living with HIV with opioid use disorders transitioning to the community: results of a double-blind, placebo-controlled randomized trial, J. Acquir. Immune Defic. Syndr. 78 (1) (2018) 43–53.
[21] J.I. Tsui, J.L. Evans, P.J. Lum, J.A. Hahn, K. Page, Association of opioid agonist therapy with lower incidence of hepatitis C virus infection in young adult injection drug users, JAMA Intern. Med. 174 (12) (2014) 1974–1981.
[22] S.A. Springer, J. Qiu, A.S. Saber-Tehrani, F.L. Altice, Retention on buprenorphine is associated with high levels of maximal viral suppression among HIV-infected opioid dependent released prisoners, PLoS One 7 (5) (2012), e38335.
[23] N. Seval, E. Eaton, S.A. Springer, Beyond antibiotics: a practical guide for the infectious disease physician to treat opioid use disorder in the setting of associated infectious diseases, Open Forum Infect. Dis. 7 (1) (2020), ofz539.
[24] M.R. Lofwall, S.L. Walsh, E.V. Nunes, et al., Weekly and monthly subcutaneous buprenorphine depot formulations vs daily sublingual buprenorphine with naloxone for treatment of opioid use disorder: a randomized clinical trial, JAMA Intern. Med. 178 (6) (2018) 764–773.
[25] B.R. Haight, S.M. Learned, C.M. Laffont, et al., Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial, Lancet (London, England) 393 (10173) (2019) 778–790.
[26] G. D'Onofrio, P.G. O'Connor, M.V. Pantalon, et al., Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial, Jama 313 (16) (2015) 1636–1644.
[27] J.M. Liebschutz, D. Crooks, D. Herman, et al., Buprenorphine treatment for hospitalized, opioid-dependent patients: a randomized clinical trial, JAMA Intern. Med. 174 (8) (2014) 1369–1376.
[28] Diagnostic and Statistical Manual of Mental Disorders: Diagnostic and Statistical Manual of Mental Disorders, Fifth ed., American Psychiatric Association, Arlington, VA, 2013.
[29] K. Iversen, N. Ihlemann, S.U. Gill, et al., Partial oral versus intravenous antibiotic treatment of endocarditis, N. Engl. J. Med. 380 (5) (2019) 415–424.
[30] H.K. Li, I. Rombach, R. Zambellas, et al., Oral versus intravenous antibiotics for bone and joint infection, N. Engl. J. Med. 380 (5) (2019) 425–436.
[31] D.R. Wesson, W. Ling, The clinical opiate withdrawal scale (COWS), J. Psychoactive Drugs 35 (2) (2003) 253–259.
[32] M.A. Ramsay, T.M. Savege, B.R. Simpson, R. Goodwin, Controlled sedation with alphaxalone-alphadolone, Br. Med. J. 2 (5920) (1974) 656–659.
[33] L. Sobell, M. Sobell, Timeline followback: a technique for assessing self-reported ethanol consumption, in: J. A, R.Z. L (Eds.), Measuring Alcohol Consumption: Psychosocial and Biological Methods, Humana Press, Totowa, NJ, 1992, pp. 41–72.
[34] M.B. Sobell, L.C. Sobell, An excellent springboard, Addiction 95 (11) (2000) 1712–1715.
[35] D.V. Sheehan, Y. Lecrubier, K.H. Sheehan, et al., The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10, J. Clin. Psychiatry 59 (Suppl. 20) (1998) 22–33 (quiz 34–57).
[36] J.B. Saunders, O.G. Aasland, T.F. Babor, J.R. de la Fuente, M. Grant, Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption–II, Addiction (Abingdon, England) 88 (6) (1993) 791–804.
[37] K. Kroenke, R.L. Spitzer, J.B. Williams, The PHQ-9: validity of a brief depression severity measure, J. Gen. Intern. Med. 16 (9) (2001) 606–613.
[38] R.L. Spitzer, K. Kroenke, J.B. Williams, Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire, JAMA 282 (18) (1999) 1737–1744.
[39] C.A. Blevins, F.W. Weathers, M.T. Davis, T.K. Witte, J.L. Domino, The posttraumatic stress disorder checklist for DSM-5 (PCL-5): development and initial psychometric evaluation, J. Trauma. Stress. 28 (6) (2015) 489–498.
[40] R.C. Kessler, L. Adler, M. Ames, et al., The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population, Psychol. Med. 35 (2) (2005) 245–256.
[41] World Health Organization Quality of Life Group, Development of the World Health Organization WHOQOL-BREF quality of life assessment, Psychol. Med. 28 (1998) 351–558.
[42] K.M. Feldhaus, J. Koziol-McLain, H.L. Amsbury, I.M. Norton, S.R. Lowenstein, J. T. Abbott, Accuracy of 3 brief screening questions for detecting partner violence in the emergency department, Jama 277 (17) (1997) 1357–1361.
[43] C. van Walraven, P.C. Austin, A. Jennings, H. Quan, A.J. Forster, A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data, Med. Care 47 (6) (2009) 626–633.
[44] E.E. Krebs, K.A. Lorenz, M.J. Bair, et al., Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference, J. Gen. Intern. Med. 24 (6) (2009) 733–738.
[45] Seek, test, treat and retain for vulnerable populations: data harmonization measure, HIV Risk Behav. https://www.drugabuse.gov/sites/default/files/HIV_Risk_BehaviorsV.pdf. (Accessed January 3, 2021).
[46] http://www.orasure.com/products-infectious/products-infectious.asp.
[47] R.E. Glasgow, T.M. Vogt, S.M. Boles, Evaluating the public health impact of health promotion interventions: the RE-AIM framework, Am. J. Public Health 89 (9) (1999) 1322–1327.
[48] J.J. Mariani, A. Mahony, M.N. Iqbal, S.X. Luo, N.H. Naqvi, F.R. Levin, Case series: rapid induction onto long acting buprenorphine injection for high potency synthetic opioid users, Am. J. Addict. 29 (4) (2020 Jul) 345–348.
[49] D.P. Alford, C.T. LaBelle, N. Kretsch, et al., Collaborative care of opioid-addicted patients in primary care using buprenorphine: five-year experience, Arch. Intern. Med. 171 (5) (2011) 425–431.
[50] C.T. LaBelle, S.C. Han, A. Bergeron, J.H. Samet, Office-based opioid treatment with buprenorphine (OBOT-B): statewide implementation of the Massachusetts collaborative care model in community health centers, J. Subst. Abus. Treat. 60 (2016) 6–13.
[51] D.A. Fiellin, M.V. Pantalon, M.C. Chawarski, et al., Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence, N. Engl. J. Med. 355 (4) (2006) 365–374.

[52] A. Di Paola, T. Lincoln, D.J. Skiest, M. Desabrais, F.L. Altice, S.A. Springer, Design and methods of a double blind randomized placebo-controlled trial of extended-release naltrexone for HIV-infected, opioid dependent prisoners and jail detainees who are transitioning to the community, Contemp. Clin. Trials 39 (2) (2014) 256–268.
[53] B.A. Johnson, N. Ait-Daoud, J.D. Roache, The COMBINE SAFTEE: a structured instrument for collecting adverse events adapted for clinical studies in the alcoholism field, J. Stud. Alcohol Suppl. 15 (2005) 157–167 (discussion 140).
[54] J. Levine, N.R. Schooler, SAFTEE: a technique for the systematic assessment of side effects in clinical trials, Psychopharmacol. Bull. 22 (2) (1986) 343–381.
[55] J.D. Lee, E.V. Nunes Jr., P. Novo, et al., Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial, Lancet 391 (10118) (2018 Jan 27) 309–318.
[56] J.D. Lee, P.D. Friedmann, T.W. Kinlock, et al., Extended-release naltrexone to prevent opioid relapse in criminal justice offenders, N. Engl. J. Med. 374 (13) (2016) 1232–1242.
[57] L. Weiss, J. Netherland, J.E. Egan, et al., Integration of buprenorphine/naloxone treatment into HIV clinical care: lessons from the BHIVES collaborative, J. Acquir. Immune Defic. Syndr. 56 (Suppl. 1) (2011) S68–S75.
[58] Y.I. Hser, E. Evans, D. Huang, et al., Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial, Addiction 111 (4) (2016) 695–705.
[59] Y.I. Hser, D. Huang, A.J. Saxon, et al., Distinctive trajectories of opioid use over an extended follow-up of patients in a multisite trial on buprenorphine + naloxone and methadone, J. Addict. Med. 11 (1) (2017) 63–69.
[60] R.D. Weiss, J.S. Potter, D.A. Fiellin, et al., Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial, Arch. Gen. Psychiatry 68 (12) (2011) 1238–1246.
[61] R.D. Weiss, J.S. Potter, M.L. Griffin, et al., Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study, Drug Alcohol Depend. 150 (2015) 112–119.
[62] R.J.A. Little, D.B. Rubin, Statistical Analysis With Missing Data, 2nd edition, 2002.
[63] Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency - Guidance for Industry, Investigators, and Institutional Review Boards. https://www.fda.gov/media/136238/download, 2020 (Accessed January 3, 2021).
[64] Infection Control Guidance for Healthcare Professionals about Coronavirus (COVID-19). https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control.html (Accessed January 3, 2021).
[65] The Management of Substance Abuse Use Disorders Working Group. VA/DoD Clinical Practice Guidelines for Management of Substance Use Disorders (SUD), The Office of Quality and Safety VA Washington DC, Quality Management Division United States Army MEDCOM, Washington DC, 2015, pp. 1–169.
[66] A.R. Williams, E.V. Nunes, A. Bisaga, F.R. Levin, M. Olfson, Development of a Cascade of care for responding to the opioid epidemic, Am. J. Drug Alcohol Abuse 45 (1) (2019) 1–10.
[67] Opportunities to Improve Opioid Use Disorder and Infectious Disease Services: Integrating Responses To a Dual Epidemic, National Academies of Sciences, Engineering, and Medicine, Washington, DC, 2020.
[68] T.A. Schwetz, T. Calder, E. Rosenthal, S. Kattakuzhy, A.S. Fauci, Opioids and infectious diseases: a converging public health crisis, J. Infect. Dis. 220 (3) (2019) 346–349.
[69] SAMSHSA, Buprenorphine, Substance Abuse and Mental Health Services Administration, Rockville, MD, 2015.
[70] A. Manhapra, R. Rosenheck, D.A. Fiellin, Opioid substitution treatment is linked to reduced risk of death in opioid use disorder, BMJ (Clinical research ed.) 357 (2017), j1947.
[71] A.Y. Walley, J.K. Alperen, D.M. Cheng, et al., Office-based management of opioid dependence with buprenorphine: clinical practices and barriers, J. Gen. Intern. Med. 23 (9) (2008) 1393–1398.
[72] A.C. Brooks, S.D. Comer, M.A. Sullivan, et al., Long-acting injectable versus oral naltrexone maintenance therapy with psychosocial intervention for heroin dependence: a quasi-experiment, J. Clin. Psychiatry 71 (10) (2010) 1371–1378.
[73] G.K. Hulse, N. Morris, D. Arnold-Reed, R.J. Tait, Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone, Arch. Gen. Psychiatry 66 (10) (2009) 1108–1115.
[74] C. Leucht, S. Heres, J.M. Kane, W. Kissling, J.M. Davis, S. Leucht, Oral versus depot antipsychotic drugs for schizophrenia—a critical systematic review and meta-analysis of randomised long-term trials, Schizophr. Res. 127 (1–3) (2011) 83–92.
[75] B. Winner, J.F. Peipert, Q. Zhao, et al., Effectiveness of long-acting reversible contraception, N. Engl. J. Med. 366 (21) (2012) 1998–2007.
[76] I. Slough, INDIVIOR PLC Results from the Phase 3 Pivotal Study of RBP-6000 Buprenorphine Monthly Depot for the Treatment of Opioid Use Disorder. Conference on Problem of Drug Dependence (CPDD), 2017 (Montreal, Canada).
[77] TIP 63, Medications for Opioid Use Disorder For Healthcare and Addiction Professionals, Policymakers, Patients, and Families, SAMHSA, 2019.