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Complete List of Authors:	Melnick, Edward; Yale University, Emergency Medicine Jeffery, Molly; Mayo Clinic, Department of Emergency Medicine Dziura, James; Yale University School of Medicine, Department of Emergency Medicine Mao, Jodi; Eastern Virginia Medical School Hess, Erik; University of Alabama at Birmingham School of Medicine, Department of Emergency Medicine Platts-Mills, Timothy; University of North Carolina School of Medicine, Department of Emergency Medicine Solad, Yauheni; Yale New-Haven Health Paek, Hyung; Yale New-Haven Health, Information Technology Services Martel, Shara; Yale University School of Medicine, Department of Emergency Medicine Patel, Mehul; University of North Carolina at Chapel Hill School of Medicine, Department of Emergency Medicine Bankowski, Laura; Yale University School of Medicine, Department of Emergency Medicine Lu, Charles; Yale University School of Medicine, Yale Center for Medical Informatics Brandt, Cynthia; Yale University School of Medicine, Yale Center for Medical Informatics, Department of Emergency Medicine D'Onofrio, Gail ; Yale University School of Medicine, Department of Emergency Medicine
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User-Centered Clinical Decision Support to Implement Emergency Department-Initiated Buprenorphine for Opioid Use Disorder: Protocol for the Pragmatic Group Randomized EMBED Trial

Edward R. Melnick, MD, MHS[1]; Molly M. Jeffery, PhD[2]; James D. Dziura, PhD, MPH[1]; Jodi A. Mao[3]; Erik P. Hess, MD, MSc[4]; Timothy F. Platts-Mills, MD, MSc[5]; Yauheni Solad, MD, MHS[6]; Hyung Paek, MD, MSEE[6]; Shara Martel[1]; Mehul D. Patel, PhD[5]; Laura Bankowski[1]; Charles C. Lu[7]; Cynthia Brandt, MD, MPH[1,7]; Gail D'Onofrio, MD, MS[1]

[1] Department of Emergency Medicine, Yale University School of Medicine, New Haven, CT
[2] Department of Emergency Medicine, Mayo Clinic, Rochester, MN
[3] Eastern Virginia Medical School, Norfolk, VA
[4] Department of Emergency Medicine, University of Alabama at Birmingham School of Medicine, Birmingham, AL
[5] Department of Emergency Medicine, University of North Carolina School of Medicine, Chapel Hill, NC
[6] Yale New-Haven Health, Information Technology Services, New Haven, CT
[7] Yale Center for Medical Informatics, Yale University School of Medicine, New Haven, CT

Corresponding Author:
Edward R. Melnick, MD
Department of Emergency Medicine
Yale School of Medicine
464 Congress Ave, Suite 260
New Haven, CT 06519
Telephone (203) 785-5174
Fax (203) 785-4580
e-mail: edward.melnick@yale.edu

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ABSTRACT

Introduction

The goal of this trial is to determine whether implementation of a user-centered clinical decision support (CDS) system can increase adoption of initiation of buprenorphine into the routine emergency care of individuals with Opioid Use Disorder (OUD).

Methods

A pragmatic cluster randomized trial is planned to be carried out in 20 Emergency Departments (EDs) across five healthcare systems over 18 months. The intervention consists of a user-centered CDS integrated into ED clinician electronic workflow and available for guidance to: 1) determine whether patients presenting to the ED meet criteria for OUD, 2) assess withdrawal symptoms, and 3) ascertain and motivate patient willingness to initiate treatment. The CDS guides the ED clinician to initiate buprenorphine and facilitate follow up. The primary outcome is the rate of buprenorphine initiated in the ED. Secondary outcomes are: 1) rates of receiving a referral, 2) fidelity with the CDS, and 3) rates of clinicians providing any ED-initiated buprenorphine, referral for ongoing treatment, and receiving Drug Addiction Act of 2000 training. Primary and secondary outcomes will be analyzed using generalized linear mixed models, with fixed effects for intervention status (CDS vs. usual care), pre-specified site and patient characteristics and random effects for study site.

Ethics and Dissemination

The protocol has been approved by the Western Institutional Review Board. No identifiable private information will be collected from patients. A waiver of informed consent was obtained for collection of data for clinician prescribing and other activities. As a minimal risk implementation study of established best practices, an Independent Study Monitor will be utilized in place of a Data Safety Monitoring Board. Results will be reported in ClinicalTrials.gov and published in open-access, peer-reviewed journals, presented at national meetings, and shared with the clinicians at participating sites via a broadcast e-mail notification of publications.

Trial registration number: clinicaltrials.gov NCT03658642

Strengths and limitations of this study:

- User-centered design of the intervention
- IT integration: perhaps largest trial of its kind integrating a similar intervention across a large number of healthcare and EHR systems. Using streamlined workflow to overcome barriers to adoption of a safe and effective treatment for opioid use disorder.
- Study design: group randomized trial shortens the study length to better control for temporal trends in the opioid epidemic. Heterogeneity of sites controlled for by constrained randomization
- Pragmatic trial: embedding intervention into routine care more likely to have an immediate impact on actual care delivery
- EHR phenotyping: establishing patient eligibility for the intervention via phenotyping permits passive data collection from EHR

INTRODUCTION

Background & Rationale

Dependence on opioids is a major public health problem in the United States, taking a devastating toll on Americans, their families, and communities.[1,2] An estimated 2.1 million people in the U.S. have opioid use disorder (OUD)[3] and more than 33,000 opioid-related deaths occur annually.[4] In 2011, there were 605,000 ED visits related to opioids in the United States.[5] From 2016-2017, emergency departments (EDs) experienced a 30% increase in visits for opioid overdose.[6] The ED offers a unique treatment opportunity for patients receiving care for acute and comorbid conditions related to opioid use.

One of the most promising treatments for OUD is buprenorphine/naloxone (BUP), a partial opioid agonist combined with an antagonist, that can be prescribed by an appropriately trained clinician in an office setting for use at home. BUP decreases mortality as well as symptoms of withdrawal, craving, and opioid use.[7,8] In a placebo-controlled randomized trial of 40 OUD patients who all received cognitive-behavioral group therapy, weekly individual counseling, and weekly urine drug screening, cumulative retention in treatment at one year was 75% for individuals in the BUP group compared to 0% in the placebo group ($p = 0.0001$).[9] A recent Cochrane review including 31 trials with 5430 participants found high quality evidence that BUP is superior to placebo in retention of participants in treatment and can reduce illicit opioid use effectively compared to placebo.[10]

Currently, ED clinicians often refer patients with OUD to opioid treatment programs rather than initiating medication for OUD (MOUD) treatment in the ED. In a randomized clinical trial involving 329 individuals with OUD, we found that ED-initiation of BUP with referral for ongoing MOUD treatment was superior to referral alone, resulting in nearly twice the percentage of patients who were engaged in formal addiction treatment at 30 days (78% with BUP vs 37% with referral alone vs 45% with brief intervention, $p < 0.001$) and less illicit opioid use.[11] Despite the efficacy of ED-initiated BUP with referral for ongoing MOUD treatment, it is currently not routinely offered in EDs due to medical, regulatory, and logistical barriers.[11–13] Adopting this evidence-based practice into routine care would shift the clinical practice paradigm for early OUD identification and treatment by initiating treatment at a time when the patient may be motivated and particularly vulnerable to morbidity and mortality.[14,15]

Clinical decision support (CDS), computerized tools that offer patient-specific assessments or recommendations to clinicians, represents one approach to embed this complex intervention into routine emergency care.[16,17] However, CDS faces its own challenges, including unintended consequences such as alert fatigue and increased cognitive load.[18–22] CDS design recommendations suggest careful consideration of the socio-technical environment and delivery of the right information, to the right person, in the right format, at the right time in clinical workflow to optimize medical decision-making.[23–26]

Objectives

For these reasons, we employed a user-centered design process to design and formatively evaluate the EMBED (Emergency Department-Initiated Buprenorphine for Opioid Use Disorder) CDS intervention. The user-centered design and formative evaluation of the EMBED intervention is reported elsewhere. Given the current opioid epidemic in the US, there is great urgency for prospective trials to identify the best approaches to BUP implementation and integration into routine practice. The goal of this multicenter, pragmatic, parallel cluster randomized trial is to compare the effectiveness of user-centered CDS for ED-initiated BUP and referral for ongoing MOUD treatment to usual care on the rates of ED initiation of BUP and referral in ED patients with OUD. We hypothesize that rates of ED-initiation of BUP and referral will be higher in the user-centered CDS arm of the trial.

Study Design

The study design is an 18-month pragmatic, parallel, cluster randomized, superiority trial using constrained randomization of clusters to arms (schematic diagram, **Figure 1**).[27–29] The unit of randomization (i.e. cluster) is the ED. EDs will be randomly allocated with an allocation ratio of 1:1. Adequate lead time will be allotted to install the intervention in the EHR at all intervention sites -- including a three month implementation and washout phase. The intervention will then begin at the same time across all sites with the CDS intervention fully implemented in the intervention sites' EHRs at the start of the trial. Clinicians at control sites will retain all control of their practice and practice as usual without the CDS intervention installed in their EHR.

Pragmatic trials study an intervention under the usual conditions in which it will be applied, as opposed to an explanatory trial which would test an intervention under ideal conditions.[27,30] In cluster randomized trials, treatment intervention is allocated to clusters (i.e. groups of individuals) rather than individuals. This is done to manipulate the physical or social

environment of the intervention when an individual intervention would likely result in contamination between intervention and control participants at the group level.[28] The parallel cluster randomized design was chosen over a stepped wedge design due to the high likelihood of confounding by temporal trends from ongoing efforts to mitigate the opioid epidemic.[31][32] A major challenge of the cluster randomized design is from potential confounding due to a limited number of heterogeneous groups.[28] Constrained randomization offers a solution to this source of confounding by balancing key cluster-level prognostic factors across the study to avoid distorting estimates of treatment effect due to the confounding factors.[29] This allocation technique more evenly distributes potential confounders between intervention arms by specifying the confounding factors, characterizing each cluster in terms of these factors, identifying a subset of randomization combinations of clusters that adequately balance confounding factors between intervention arms and randomly selecting one of these combinations as the allocation scheme.[29] Potential confounders that will be used for this trial are: EHR vendor, ED annual volume, ED type (e.g., academic, community, urban, rural, etc), ratio of ED attendings who have a waiver to prescribe BUP, current rate of ED BUP prescribing, resources in ED to facilitate management of patients with OUD, and willingness of staff to adopt the practice of ED-initiation of BUP.

METHODS

Participants

There will be 20 participating EDs from hospitals within approximately five health care systems (HCS). At the time of writing this protocol, all of the sites have very low (or 0) rates of BUP initiation in the ED. The final study sites will be determined based on sample size needs, anticipated number of eligible patients per site determined by electronic health records (EHR) phenotype,[33–36] and willingness and ability to participate (e.g., EHR integration of the intervention, EHR data extraction, availability of BUP in the ED and referral for ongoing MOUD treatment in the surrounding community). When finalized, the full study site list will be available at clinicaltrials.gov.

The intervention will be conducted at the site level. Patients are not considered human subjects since: (1) no identifiable private information will be collected, (2) the intervention does not target the patient, and (3) EHR data will be collected retrospectively without interaction with the patient. The study sample will include all ED attending physicians credentialed to practice in the study site EDs. For ED encounters with physicians who practice at both an intervention and

control site, only the encounters at intervention sites will contribute data for analyses. Encounters with these physicians at a control site will be excluded from the primary analysis.

Adult ED patients (age 18 years or older) meeting an EHR-derived phenotype suggesting possible OUD will be included in the analysis: those who are discharged from the ED, not pregnant, and not currently taking a MOUD. The initial phenotype has been developed by the study team and is currently undergoing validation via emergency physician chart review to determine the phenotype's validity in identifying the target patient population.[33] Details of this phenotype and its validation will be reported separately. All ED patients meeting the EHR phenotype criteria will be eligible for the trial. For patients with more than one ED visit during the study period, only the initial ED visit will be eligible for inclusion in the primary analysis. The CDS will also be available for all clinicians on the care team and to use for patients who are not identified by the phenotype. These patients will be excluded from the primary analyses.

Intervention

The intervention for this study includes the user-centered CDS as well as education of ED clinicians practicing at all study sites.

The need for flexibility in the graphical user interface of the intervention resulted in the decision to develop the CDS as a web application. This provides the ability to access the tool both embedded within the EHR or directly over the Internet. The web application was developed as a single-page application (SPA) based on React JavaScript library. The CDS is a user-initiated activity in the EHR that calls the web application using Active Guidelines to streamline the flow diagram of our clinical protocol for ED-initiated BUP (**Figure 2)**.[37]

The intervention's graphical user interface (**Figure 3**) is an intuitive, simple layout presenting four care pathways in columns based on the patient's diagnosis of OUD, the severity of withdrawal, and readiness to start treatment. There is additional, optional decision support available for guidance to: 1) evaluate OUD severity based on DSM-5 criteria, 2) assess withdrawal severity using the clinical opiate withdrawal scale (COWS) score, and 3) motivate patient willingness and readiness to initiate MOUD treatment with a brief motivational interview.[38,39] These materials are also available to share with other members of the care team via a web address, text messaging, or QR code. The interface also includes a toggle switch for the user based on whether or not they have a waiver to prescribe BUP. Non-waivered

clinicians cannot prescribe BUP but can administer a one-time dose of BUP in the ED for up to 72-hours.[40] When integrated into the local EHR system, launching a care pathway enables the user to: place orders, refer for ongoing MOUD treatment, and update clinical notes.

The educational plan will be site-specific and tailored to the usual care at that institution. It will be administered within three months of the study start date. The details of the plan will be developed in partnership with local champions who self-identify an interest in helping to implement an ED-initiated BUP protocol at their site. Specifically, the education plan will be required to include:

1. A didactic on opioid use disorder, its diagnosis, assessment of withdrawal severity, and local resources for referral for ongoing MOUD treatment
2. Circulation and posting in each study site ED of the flow diagram of the study's clinical protocol for ED-initiated BUP (**Figure 2**). Since this protocol is considered best practice, clinicians at control sites will retain all control of their practice and be encouraged to follow this protocol even though the CDS will not be available to them.
3. Intervention sites will include strategies to increase use of the intervention by training clinicians on how to launch and use the CDS. Use of the intervention will be tracked with site-specific audit and feedback that is consistent with typical quality improvement initiatives at that site.

Given the ongoing and escalating opioid epidemic and wide scope of this trial, we anticipate that there may be concomitant interventions to stem OUD at study sites during the trial. We plan to permit these interventions as long as they are: (1) implemented before randomization so that they can be tracked and accounted for in the constrained randomization process, and (2) they are not a health IT intervention targeted at clinicians to initiate BUP in the ED.

Outcomes

The primary study hypothesis is that there will be higher rates of ED-initiated BUP with referral for ongoing MOUD with user-centered CDS compared with usual care. Therefore, the primary outcome will be BUP initiation in the ED, defined as whether or not an eligible patient is administered BUP in the ED and/or prescribed BUP upon discharge from the ED. Although this is not a patient-centered outcome, it is a pragmatic and meaningful surrogate that will serve as a lead indicator of the CDS intervention's effect on engaging more OUD patients in treatment.

We will also evaluate the effect of user-centered CDS on the following secondary implementation outcomes as compared to usual care, informed by the RE-AIM framework:[41,42]

1. Referral to follow-up for ongoing MOUD treatment (patient-level; Y/N)
2. Prescription for naloxone at ED discharge (patient-level; Y/N)
3. Receipt of discharge instructions on opioid use, overdose education, naloxone education, and buprenorphine education (patient-level; Y/N)
4. Attending physician adoption rates (physician level):
   a. Provision of any ED-initiated BUP during the trial (Y/N)
   b. Provision of any referral for ongoing MOUD treatment during the trial (Y/N)
5. Receipt of Drug Addiction Treatment Act of 2000 training during trial (clinician level; Y/N)

Additional secondary implementation outcomes to be obtained from the web application include: clinician fidelity with the intervention assessed via a critical action checklist[43] and error rate of the intervention (using surrogates based on tool usage, e.g., application launched but not used, launching a page in the web application and spending less than two seconds on that page). The intervention will continue to be made available for use after the trial concludes; three months after trial completion, medical record review of eligible patients will be conducted at a subset of intervention sites to determine the maintenance rate of the intervention.

Sample Size

Current rates of BUP use in the ED range from 0-2% with most sites at 0%. Assuming a rate of BUP use in the usual care group of 1%, an increase to 10% would be a convincing and meaningful incremental effect of the intervention. Preliminary data from EDs that will be randomized in this trial suggest an Intraclass Correlation Coefficient (ICC) for BUP use of 0.01. The NIH group randomized sample size calculator[44] was used to determine the required number of sites to be randomized. With a two-sided type I error of 0.05, a conservative ICC of 0.03, and an expected average of 200 participants per site, a total of 12 sites will provide 90% power to detect a difference of 9%. This estimate is based on the assumption that all sites will have at least 200 unique patient visits during the trial that meet the EHR phenotype.

We estimated the impact of enrollment variability across sites on the required sample size using the formula described by Eldridge et al.[45] We added 2 sites to the total number of sites given the use of z-scores rather than t-scores in the estimation. As the coefficient of variation (CV) in the number of participants enrolled across sites increases, the required number of sites

increases (**Figure 4**). To accommodate this potential variability, we will randomize a total of 20 sites.

Table 1 shows the power to detect different effect sizes given randomization of 20 sites. Even with large variability in participant enrollment (CV=1), we will have over 90% power to detect a difference of 0.09. We will have good power (>80%) to detect effect sizes as low as 0.05 provided the variability in site enrollment is not great (<0.50).

	Effect Size (Difference in Proportions)					
Coefficient of Variation in Enrollment		**0.05**	**0.06**	**0.07**	**0.08**	**0.09**
	0	87%	94%	97%	99%	99%
	0.2	86%	93%	97%	99%	99%
	0.5	80%	89%	94%	97%	98%
	0.8	70%	80%	87%	92%	95%
	1.0	62%	72%	80%	87%	91%

Allocation

Study sites that meet readiness criteria at the time of randomization will be allocated 1:1 to CDS and usual care groups using constrained randomization conducted by personnel in the data coordinating center (DCC). The general method will follow procedures and recommendations from the literature on group randomized trials.[29]

With a small number of sites that differ in important ways, unconstrained randomization may not adequately balance important site characteristics. To improve comparability of treatment and control sites, personnel in the DCC under the direction of JDD will list all possible allocations of treatment and control groups (with 20 sites, there are about 165,000 combinations of treatment and control groups). The imbalance score (□) from Raab and Butcher will be calculated for each possible allocation.[46]

$$\beta = \sum_{l=1}^{S} \omega_l (\overline{x}_{0l} - \overline{x}_{1l})^2$$

where *S* is the number of variables on which the groups should be balanced, ω_l is a weight calculated as the inverse variance of the mean of variable *l* across the hospitals, and the $\overline{x_l}$ represent the means of variable *l* across the hospitals in the intervention (indexed as 1) and

control (indexed as 0) groups. A candidate set of 1000 possible allocations with the most favorable imbalance scores will be selected, and the final allocation will be selected at random from that candidate set.

Since clinicians must know how to launch and use the intervention, they will not be blinded to the allocation of their site as a control or intervention site. Clinicians may inform patients that they are using the CDS or not, as they deem appropriate consistent with CDS use in their usual practice. All study sites will post information in their ED informing patients of the study.

Data Collection

Outcome data will be collected via SQL query of the local EHR at regular intervals from data routinely collected in each hospital's EHR. This will facilitate large-scale data collection that would not otherwise be practical in an explanatory trial.

To enable consistent EHR data collection across sites, a master data dictionary of all data elements will be created. At each study site, the variables in the data dictionary will be validated against the institutional EHR to ensure that the variables are correctly mapped to the EHR field that corresponds to the clinical intent of the variable after accounting for documentation practices and workflow at each site.[47] For data quality assurance, the mapped variables will be validated against the EHR to ensure that the data are clinically relevant to the goals of the project and correctly represents the clinical data that clinicians use to make decisions. Additionally, data to determine compliance, use, and fidelity with the CDS intervention that could not be reliably abstracted from the EHR (e.g., DSM-5 OUD score, COWS score) will be abstracted from the web application's use logs. Information on whether the patient attended the referred follow-up visit and whether the patient was prescribed BUP as an outpatient will be abstracted from the EHR if available (e.g., if the patient is seen for follow-up within the same system).

Data will be sent from study sites to the study DCC at predetermined, regular intervals. The DCC will conduct ongoing data monitoring activities on study data from all participating sites to ensure data received is what it is intended to be. Baseline data for the study participants will include demographic and clinical data such as age, gender, race, ethnicity, insurance status, past medical and psychiatric history, recent medical or psychiatric hospital admissions, recent

enrollment in formal addiction treatment, active prescriptions for other opioids, and urine drug screen results as ascertained by regularly collected data in the EHR.

Data Management

Study data will only be available to members of the study DCC who are authorized for this study. To ensure the privacy and confidentiality of data for this project, DCC servers hosting data repositories are strongly firewalled; access to the repositories is permitted only through properly authenticated Web APIs. All data will be encrypted both at rest and in transit. The DCC database-hosting is certified by our institution's Information Security Office as conforming to HIPAA and our institution's data protection guidelines. All project computers are stored in locked offices within a building having limited, electronic passkey access. All computers are password protected and protected by our institution's firewall which is encrypted using Microsoft BitLocker. Individually identifiable or deducible data will only be by transmitted via secured telecommunications, never by unsecured telecommunications like email or electronic File Transfer Protocol (FTP). Procedures are in place for rapid recovery from hardware or database failure.

Data Monitoring

As a minimal risk implementation study of established best practices, an Independent Study Monitor will be utilized in place of a formal Data Safety Monitoring Board (DSMB). Interim monitoring will focus on adherence to the protocol, completeness of data retrieval from each ED's EHR, and uptake of the CDS intervention. A set of monitoring tables will be generated for this purpose. The Independent Study Monitor will report directly to the study DCC. No interim analyses for effectiveness are planned.

Analysis Plan

General Considerations: This is a cluster randomized trial to test the hypothesis that there will be higher rates of provision of ED-initiated BUP and referral for ongoing MOUD with user-centered CDS compared with usual care. Analyses will be conducted as intention to treat including all individuals regardless of intervention receipt. While the unit of randomization is at the level of the ED, the unit of analysis will be the patient. Analyses of primary and secondary outcomes will be conducted using logistic regression with weighted generalized estimating equations (GEE) to account for clustering from the EDs and physicians in patient outcome models.[48] Analyses will be performed in SAS v9.4 (Cary, NC) with a two-sided type I error of

0.05 (unless otherwise specified). For the primary and secondary analyses described below, only the first ED encounter for an individual patient will be used. Supportive analyses will include patients with repeated ED visits.

Comparability of Baseline and Intervention Patients: Distributions of baseline demographic and clinical characteristics will be described during baseline and intervention periods. Comparability for continuous variables will be examined graphically and by summary statistics (means, medians, quartiles, etc.). Categorical variables will be examined by calculating frequency distributions.

Analysis of Primary Outcome: The primary outcome, initiation of BUP in the ED, will be assessed for all patients that meet the criteria for the EHR phenotype. Intervention differences (CDS vs usual care) for this dichotomous outcome will be examined using weighted GEE. The weighted GEE provides consistent parameter estimates when the dropout mechanism is correctly classified by implementing the inverse-probability weighted method to account for dropouts under the missing at random (MAR) assumption. Inverse probability weights are estimated by a logistic regression of dropout. The weighted GEE model will contain an effect for intervention (CDS vs usual care). An exchangeable working correlation will be used to account for clustering of responses within ED and physicians. The model will also include cluster-level covariates included in the constrained randomization and patient-level covariates that may be associated with the delivery of BUP (age, gender, race, ethnicity, insurance status, past medical and psychiatric history, recent medical or psychiatric hospital admissions, recent enrollment in formal addiction treatment, active prescriptions for other opioids, and urine drug screen results). Linear contrasts will be used to estimate treatment differences along with 95% confidence intervals in the proportions of ED patients that received BUP in CDS vs. usual care. Given the relative advantages of Generalized Estimating Equations, and generalized linear mixed models (GLMM) sensitivity analyses will compare treatments using a logistic regression with GLMM, with random effects for ED and physician.

Analysis of Secondary Outcomes: Secondary outcomes such as referral for MOUD appointment, attendance at an MOUD appointment (if available in the EHR), prescription for naloxone at ED discharge and receipt of discharge instructions will be evaluated using weighted weighted GEE as described above. Assessments of the physician including provision of any ED-initiated BUP during the trial, provision of any referral for ongoing MOUD treatment during

the trial and receipt of Drug Addiction Treatment Act of 2000 training during the trial will be compared between CDS and usual care using GEE. These models will be stratified by the number of eligible patients the physician encountered during the trial and will include an effect for intervention, cluster-level covariates included in the constrained randomization, and an exchangeable working correlation. Discrete numeric outcomes such as clinical fidelity will be compared using the GEE with a log link and a negative binomial distribution.

Plan for Missing Data: Several strategies will be imposed to accommodate the likelihood that missing data will occur during this study. Prevention is the most obvious and effective manner to control bias and loss of power from missing data.[49] As noted in the Data Collection section above, prior to the trial we will pilot data collection procedures. Variables with large proportions of missing will be excluded from collection. We will follow the intent to treat principle, requiring follow-up of all EDs randomized regardless of the treatment received.[50] Regular data retrieval from EHRs combined with monitoring and missing data reports will trigger protocols for tracking and obtaining missing data. Despite these prevention efforts it is reasonable to assume missing data will occur. Our primary analysis is valid under the assumption that missing data will be missing at random (MAR).[51] We will evaluate the plausibility of this assumption by determining the extent of missing data and use logistic regression to identify factors associated with missing data. As appropriate, we will conduct sensitivity analysis using pattern-mixture and selection models under missing not at random (MNAR) assumptions to examine the robustness of conclusions of the primary analysis to missing data.[49,51]

ETHICS AND DISSEMINATION

We plan to obtain all necessary regulatory and human subjects protection approvals and procedures. The protocol has been approved by the Western Institutional Review Board, central IRB (protocol number 20182278, study number 1189765). The local IRBs at each participating site will implement a reliance agreement with this central board. We anticipate a waiver of informed consent under the Common Rule (45 code of federal regulations (CFR) 46.116 given that:[52,53] (1) the research involves no more than minimal risk to the subjects;[54] (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) subjects will be provided with additional pertinent information after participation.

Patients are not considered human subjects by HHS regulation 45 CFR 46.102(f)[53] since: (1) no identifiable private information will be collected, (2) the intervention does not target the patient, and (3) EHR data will be collected retrospectively without interaction with the patient. Therefore, consent is not applicable to this population. Furthermore, all recommendations included in the CDS intervention are considered best practices in treatment of OUD. The OUD population has a high underlying risk of morbidity/mortality (approximately 5% risk of death in 12 months).[8] Patient rights and welfare will be protected per standard practice. Therefore, the risk to a patient with OUD who is not receiving MOUD treatment in their ordinary daily lives greatly exceeds the risk of the EMBED intervention. All study sites will post details about the study in a location visible to patients to make them aware of the option to receive BUP and referral to treatment so as best to offer an informed decision for requesting care. Patients will retain the right to request MOUD treatment at any study site. Patients and the public were not involved in the research design.

Clinicians at all study sites will have access to all standard OUD medications and services to which they would otherwise have access to treat OUD patients. Clinicians will retain all control of their practice and at intervention sites have the option whether or not to use the intervention (i.e., can opt out). Clinician identifiers will be collected in order to follow practice patterns. However, the investigators will be blinded to both site and clinician identifiers. Each system will use an Honest Broker to protect the welfare and identity of each site and clinician and allow adjudication for analyses. Clinicians will be made aware of the study, its outcomes, the data to be collected and, at intervention sites, how to use and opt out of using the CDS via broadcast e-mail and direct communication by site champions. A flow diagram of the study's clinical protocol (**Figure 2**) will shared with clinicians and posted in the clinical work area of all study sites. Since this protocol is considered best practice, clinicians at control sites will retain all control of their practice and be encouraged to follow this protocol even though the CDS will not be available to them. As this is a pragmatic trial focused on implementing this intervention in a way that is as close to routine care as possible, consenting clinicians would not be consistent with routine CDS implementation and could jeopardize the scientific validity of the CDS intervention to overcome barriers to adoption of this practice[52]. Given the stigma[11] associated with treating individuals with OUD, the additional burden of the consent process could be a deterrent for clinicians to provide MOUD treatment to appropriate patients and bias the sample to clinicians with less stigma toward treating these patients. For this reason and since clinician data will be de-identified and unavailable to the investigators, we propose a waiver of consent of the clinicians

to ensure the scientific validity of our findings. There is precedent for such a waiver in a similar situation.[55] Results will be published in open-access, peer-reviewed journals, presented at national meetings, and shared with the clinicians at participating sites via a broadcast email notification of publications.

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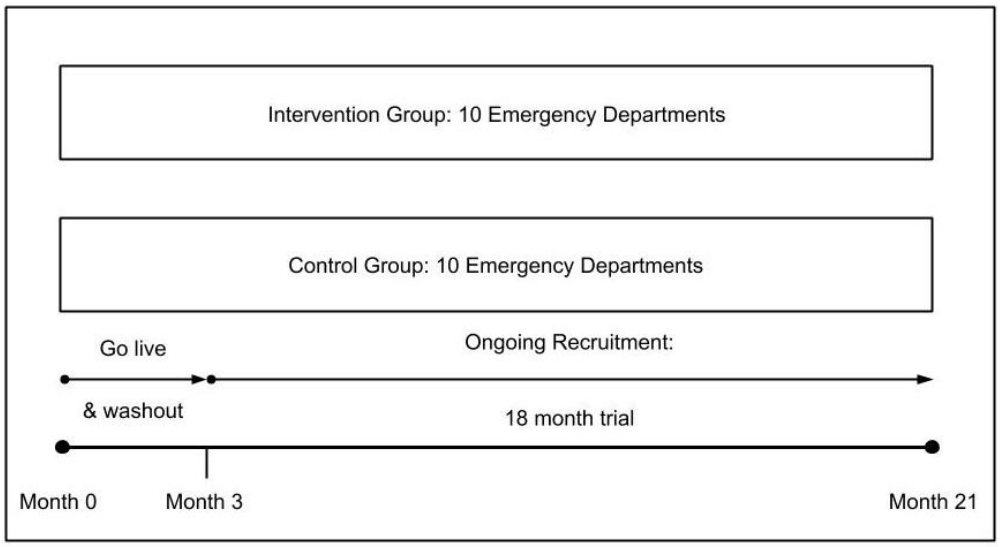
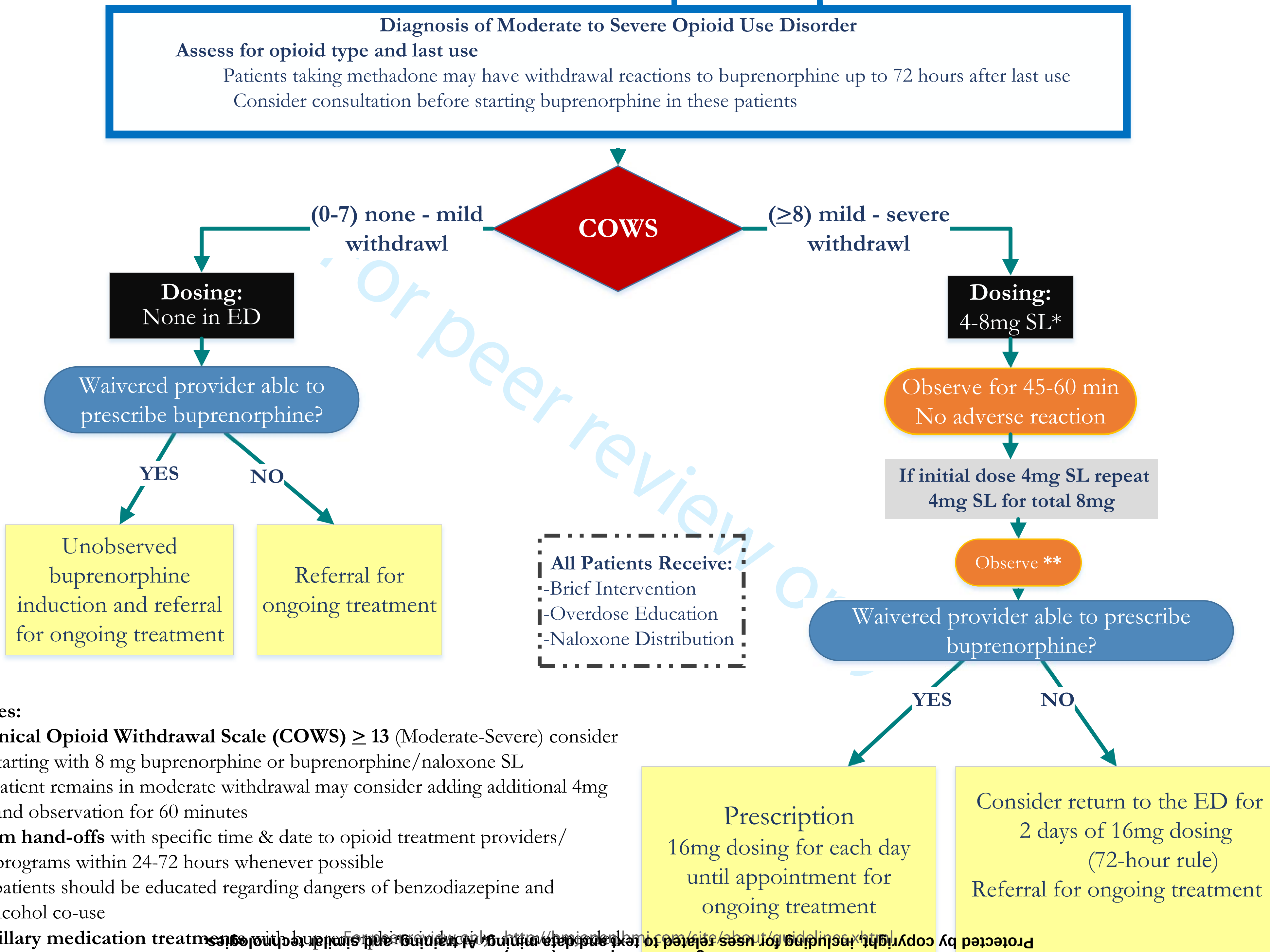


Figure 1. Schematic diagram of parallel, cluster-randomized study design

305x166mm (72 x 72 DPI)

ED-Initiated Buprenorphine



Notes:

***Clinical Opioid Withdrawal Scale (COWS) ≥ 13** (Moderate-Severe) consider starting with 8 mg buprenorphine or buprenorphine/naloxone SL

** Patient remains in moderate withdrawal may consider adding additional 4mg and observation for 60 minutes

Warm hand-offs with specific time & date to opioid treatment providers/ programs within 24-72 hours whenever possible

All patients should be educated regarding dangers of benzodiazepine and alcohol co-use

Ancillary medication treatments with bu

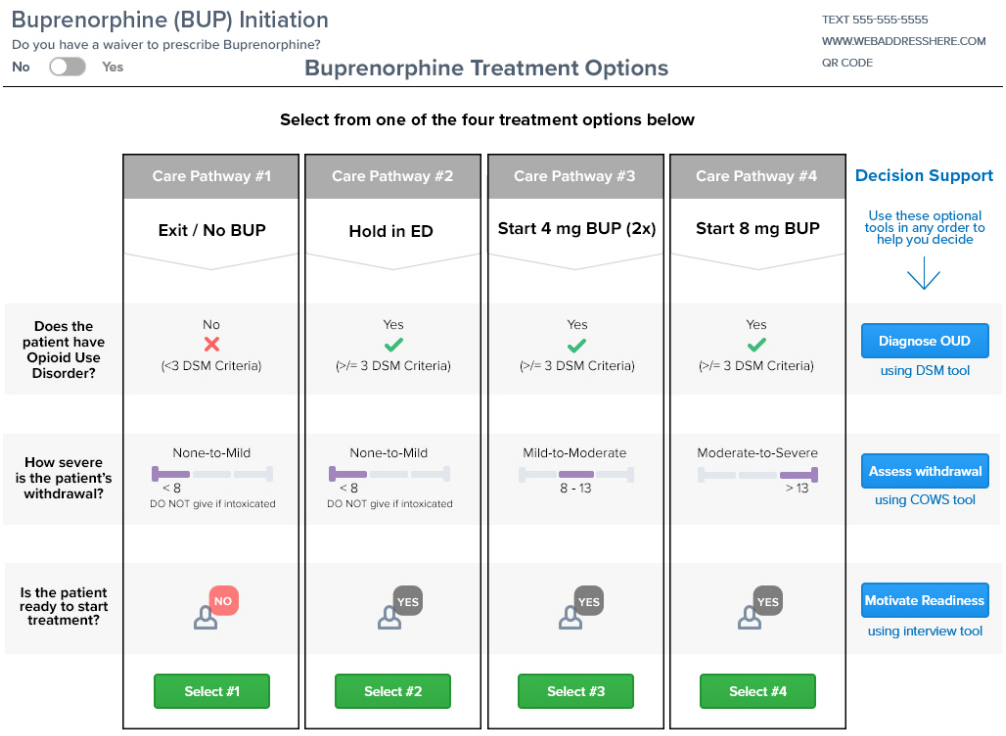


Figure 3. Graphical user interface of the user-centered CDS EMBED intervention

360x270mm (72 x 72 DPI)

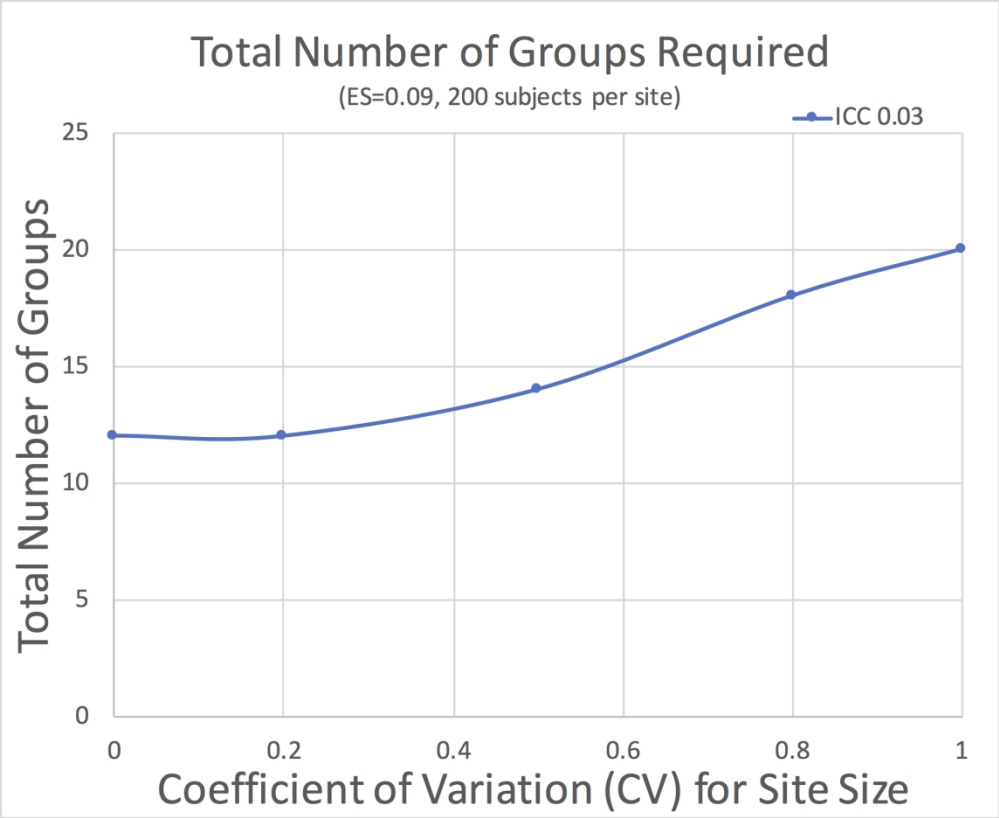


Figure 4. Number of study sites required as a function of coefficient of variation for site size assuming an ICC of 0.03

181x148mm (300 x 300 DPI)

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	13
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	N/A
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	N/A
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether analysis was by original assigned groups	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	N/A
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	N/A
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	1
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	N/A
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	11
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	N/A
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	11

BMJ Open

User-Centered Clinical Decision Support to Implement Emergency Department-Initiated Buprenorphine for Opioid Use Disorder: Protocol for the Pragmatic Group Randomized EMBED Trial

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User-Centered Clinical Decision Support to Implement Emergency Department-Initiated Buprenorphine for Opioid Use Disorder: Protocol for the Pragmatic Group Randomized EMBED Trial

Edward R. Melnick, MD, MHS[1]; Molly M. Jeffery, PhD[2]; James D. Dziura, PhD, MPH[1]; Jodi A. Mao[3]; Erik P. Hess, MD, MSc[4]; Timothy F. Platts-Mills, MD, MSc[5]; Yauheni Solad, MD, MHS[6]; Hyung Paek, MD, MSEE[6]; Shara Martel[1]; Mehul D. Patel, PhD[5]; Laura Bankowski[1]; Charles C. Lu[7]; Cynthia Brandt, MD, MPH[1,7]; Gail D'Onofrio, MD, MS[1]

[1] Department of Emergency Medicine, Yale University School of Medicine, New Haven, CT
[2] Department of Emergency Medicine, Mayo Clinic, Rochester, MN
[3] Eastern Virginia Medical School, Norfolk, VA
[4] Department of Emergency Medicine, University of Alabama at Birmingham School of Medicine, Birmingham, AL
[5] Department of Emergency Medicine, University of North Carolina School of Medicine, Chapel Hill, NC
[6] Yale New-Haven Health, Information Technology Services, New Haven, CT
[7] Yale Center for Medical Informatics, Yale University School of Medicine, New Haven, CT

Corresponding Author:
Edward R. Melnick, MD, Department of Emergency Medicine, Yale School of Medicine, 464 Congress Ave, Suite 260, New Haven, CT 06519
Telephone (203) 785-5174; Fax (203) 785-4580; e-mail: edward.melnick@yale.edu

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Author contributions: ERM and GD conceived of the work. ERM, MMJ, JDD, EPH, TPM, and GD designed the study. ERM, MMJ, EPH, TPM, YS, HP, SM, MDP, CCL, CB, and GD are responsible for the implementation of the trial. ERM, MMJ, JAM, JDD (Sample Size, Allocation, and Analysis), and LB (Ethics) drafted the initial manuscript. All authors edited and approved the final version submitted for publication. ERM takes responsibility for all aspects of the work.

ABSTRACT

Introduction

The goal of this trial is to determine whether implementation of a user-centered clinical decision support (CDS) system can increase adoption of initiation of buprenorphine into the routine emergency care of individuals with Opioid Use Disorder (OUD).

Methods

A pragmatic cluster randomized trial is planned to be carried out in 20 Emergency Departments (EDs) across five healthcare systems over 18 months. The intervention consists of a user-centered CDS integrated into ED clinician electronic workflow and available for guidance to: 1) determine whether patients presenting to the ED meet criteria for OUD, 2) assess withdrawal symptoms, and 3) ascertain and motivate patient willingness to initiate treatment. The CDS guides the ED clinician to initiate buprenorphine and facilitate follow up. The primary outcome is the rate of buprenorphine initiated in the ED. Secondary outcomes are: 1) rates of receiving a referral, 2) fidelity with the CDS, and 3) rates of clinicians providing any ED-initiated buprenorphine, referral for ongoing treatment, and receiving Drug Addiction Act of 2000 training. Primary and secondary outcomes will be analyzed using generalized linear mixed models, with fixed effects for intervention status (CDS vs. usual care), pre-specified site and patient characteristics and random effects for study site.

Ethics and Dissemination

The protocol has been approved by the Western Institutional Review Board. No identifiable private information will be collected from patients. A waiver of informed consent was obtained for collection of data for clinician prescribing and other activities. As a minimal risk implementation study of established best practices, an Independent Study Monitor will be utilized in place of a Data Safety Monitoring Board. Results will be reported in ClinicalTrials.gov and published in open-access, peer-reviewed journals, presented at national meetings, and shared with the clinicians at participating sites via a broadcast e-mail notification of publications.

Trial registration number: clinicaltrials.gov NCT03658642

Strengths and limitations of this study:

- This pragmatic trial embeds a user-centered clinical decision support tool into routine care in the emergency department, reducing negative impact on providers and increasing the likelihood of immediate impact on actual care delivery
- The streamlined workflow developed for the implementation of the intervention allows delivery across a large number of healthcare settings and across different EHR systems, increasing the generalizability of the findings
- Study length is shortened by the group-randomized design, better controlling for temporal trends in the opioid overdose epidemic
- Constrained randomization allows heterogeneity of included sites despite the small number of entities being randomized (a characteristic of group-randomized designs)
- Establishing patient eligibility for the intervention via phenotyping permits passive data collection from the EHR, reducing the reporting burden for sites

INTRODUCTION

Background & Rationale

Dependence on opioids is a major public health problem in the United States, taking a devastating toll on Americans, their families, and communities.[1,2] An estimated 2.1 million people in the U.S. have opioid use disorder (OUD)[3] and more than 33,000 opioid-related deaths occur annually.[4] In 2011, there were 605,000 ED visits related to opioids in the United States.[5] From 2016-2017, emergency departments (EDs) experienced a 30% increase in visits for opioid overdose.[6] The ED offers a unique treatment opportunity for patients receiving care for acute and comorbid conditions related to opioid use.

One of the most promising treatments for OUD is buprenorphine/naloxone (BUP), a partial opioid agonist combined with an antagonist, that can be prescribed by an appropriately trained clinician in an office setting for use at home. BUP decreases mortality as well as symptoms of withdrawal, craving, and opioid use.[7,8] In a placebo-controlled randomized trial of 40 OUD patients who all received cognitive-behavioral group therapy, weekly individual counseling, and weekly urine drug screening, cumulative retention in treatment at one year was 75% for individuals in the BUP group compared to 0% in the placebo group (p = 0.0001).[9] A recent Cochrane review including 31 trials with 5430 participants found high quality evidence that BUP is superior to placebo in retention of participants in treatment and can reduce illicit opioid use effectively compared to placebo.[10]

Currently, ED clinicians often refer patients with OUD to opioid treatment programs rather than initiating medication for OUD (MOUD) treatment in the ED. In a randomized clinical trial involving 329 individuals with OUD, we found that ED-initiation of BUP with referral for ongoing MOUD treatment was superior to referral alone, resulting in nearly twice the percentage of patients who were engaged in formal addiction treatment at 30 days (78% with BUP vs 37% with referral alone vs 45% with brief intervention, p < 0.001) and less illicit opioid use.[11] Despite the efficacy of ED-initiated BUP with referral for ongoing MOUD treatment, it is currently not routinely offered in EDs due to medical, regulatory, and logistical barriers.[11–13] Adopting this evidence-based practice into routine care would shift the clinical practice paradigm for early OUD identification and treatment by initiating treatment at a time when the patient may be motivated and particularly vulnerable to morbidity and mortality.[14,15]

Clinical decision support (CDS), computerized tools that offer patient-specific assessments or recommendations to clinicians, represents one approach to embed this complex intervention into routine emergency care.[16,17] However, CDS faces its own challenges, including unintended consequences such as alert fatigue and increased cognitive load.[18–22] CDS design recommendations suggest careful consideration of the socio-technical environment and delivery of the right information, to the right person, in the right format, at the right time in clinical workflow to optimize medical decision-making.[23–26]

Objectives

For these reasons, we employed a user-centered design process to design and formatively evaluate the EMBED (Emergency Department-Initiated Buprenorphine for Opioid Use Disorder) CDS intervention. The user-centered design and formative evaluation of the EMBED intervention is reported elsewhere. Given the current opioid epidemic in the US, there is great urgency for prospective trials to identify the best approaches to BUP implementation and integration into routine practice. The goal of this multicenter, pragmatic, parallel cluster randomized trial is to compare the effectiveness of user-centered CDS for ED-initiated BUP and referral for ongoing MOUD treatment to usual care on the rates of ED initiation of BUP and referral in ED patients with OUD. We hypothesize that rates of ED-initiation of BUP and referral will be higher in the user-centered CDS arm of the trial.

Study Design

The study design is an 18-month pragmatic, parallel, cluster randomized, superiority trial using constrained randomization of clusters to arms (schematic diagram, **Figure 1**).[27–29] The unit of randomization (i.e. cluster) is the ED. EDs will be randomly allocated with an allocation ratio of 1:1. Adequate lead time will be allotted to install the intervention in the EHR at all intervention sites -- including a three month implementation and washout phase. The intervention will then begin at the same time across all sites with the CDS intervention fully implemented in the intervention sites' EHRs at the start of the trial. Clinicians at control sites will retain all control of their practice and practice as usual without the CDS intervention installed in their EHR.

Pragmatic trials study an intervention under the usual conditions in which it will be applied and generally use usual care as the comparator, as opposed to an explanatory trial which would test an intervention under ideal conditions,.[27,30,31] In cluster randomized trials, treatment

intervention is allocated to clusters (i.e. groups of individuals) rather than individuals. This is done to manipulate the physical or social environment of the intervention when an individual intervention would likely result in contamination between intervention and control participants at the group level.[28] The parallel cluster randomized design was chosen over a stepped wedge design due to the high likelihood of confounding by temporal trends from ongoing efforts to mitigate the opioid epidemic.[32][33] A major challenge of the cluster randomized design is from potential confounding due to a limited number of heterogeneous groups.[28] Constrained randomization offers a solution to this source of confounding by balancing key cluster-level prognostic factors across the study to avoid distorting estimates of treatment effect due to the confounding factors.[29] This allocation technique more evenly distributes potential confounders between intervention arms by specifying the confounding factors, characterizing each cluster in terms of these factors, identifying a subset of randomization combinations of clusters that adequately balance confounding factors between intervention arms and randomly selecting one of these combinations as the allocation scheme.[29] Potential confounders that will be used for this trial are: EHR vendor, ED annual volume, ED type (e.g., academic, community, urban, rural, etc), ratio of ED attendings who have a waiver to prescribe BUP, current rate of ED BUP prescribing, resources in ED to facilitate management of patients with OUD, and willingness of staff to adopt the practice of ED-initiation of BUP.

METHODS

Participants

There will be 20 participating EDs from hospitals in the United States within approximately five health care systems (HCS). At the time of writing this protocol, all of the sites have very low (or 0) rates of BUP initiation in the ED. The final study sites will be determined based on sample size needs, anticipated number of ED patients with OUD per site determined by electronic health records (EHR) phenotype,[34–37] and willingness and ability to participate (e.g., EHR integration of the intervention, EHR data extraction, availability of BUP in the ED and referral for ongoing MOUD treatment in the surrounding community). When finalized, the full study site list will be available at clinicaltrials.gov.

The intervention will be conducted at the site level. Patients are not considered human subjects since: (1) no identifiable private information will be collected, (2) the intervention does not target the patient, and (3) EHR data will be collected retrospectively without interaction with the patient. The study sample will include all ED attending physicians credentialed to practice in the

study site EDs. For ED encounters with physicians who practice at both an intervention and control site, only the encounters at intervention sites will contribute data for analyses. Encounters with these physicians at a control site will be excluded from the primary analysis.

Encounters with adult ED patients (age 18 years or older) meeting an EHR-derived phenotype suggesting possible OUD will be included in the analysis: those who are discharged from the ED, not pregnant, and not currently taking a MOUD. The initial phenotype has been developed by the study team and is currently undergoing validation via emergency physician chart review to determine the phenotype's validity in identifying the target patient population.[34] Details of this phenotype and its validation will be reported separately. All encounters with ED patients meeting the EHR phenotype criteria will be eligible for the trial. For patients with more than one ED visit during the study period, only the initial ED visit will be eligible for inclusion in the primary analysis. The CDS will also be available for all clinicians on the care team and to use for encounters with patients who are not identified by the phenotype. These encounters will be excluded from the primary analyses.

Intervention

The intervention for this study includes the user-centered CDS as well as education of ED clinicians practicing at all study sites.

The need for flexibility in the graphical user interface of the intervention resulted in the decision to develop the CDS as a web application. This provides the ability to access the tool both embedded within the EHR or directly over the Internet. The web application was developed as a single-page application (SPA) based on React JavaScript library. The CDS is a user-initiated activity in the EHR that calls the web application using Active Guidelines to streamline the flow diagram of our clinical protocol for ED-initiated BUP (**Figure 2)**.[38]

The intervention's graphical user interface (**Figure 3**) is an intuitive, simple layout presenting four care pathways in columns based on the patient's diagnosis of OUD, the severity of withdrawal, and readiness to start treatment. There is additional, optional decision support available for guidance to: 1) evaluate OUD severity based on DSM-5 criteria, 2) assess withdrawal severity using the clinical opiate withdrawal scale (COWS) score, and 3) motivate patient willingness and readiness to initiate MOUD treatment with a brief motivational interview.[39,40] These materials are also available to share with other members of the care

team via a web address, text messaging, or QR code. The interface also includes a toggle switch for the user based on whether or not they have a waiver to prescribe BUP. Non-waivered clinicians cannot prescribe BUP but can administer a one-time dose of BUP in the ED for up to 72-hours.[41] When integrated into the local EHR system, launching a care pathway enables the user to: place orders, refer for ongoing MOUD treatment, and update clinical notes.

The educational plan will be site-specific and tailored to the usual care at that institution. It will be administered within three months of the study start date. The details of the plan will be developed in partnership with local champions who self-identify an interest in helping to implement an ED-initiated BUP protocol at their site. Specifically, the education plan will be required to include:

1. A didactic on opioid use disorder, its diagnosis, assessment of withdrawal severity, and local resources for referral for ongoing MOUD treatment
2. Circulation and posting in each study site ED of the flow diagram of the study's clinical protocol for ED-initiated BUP (**Figure 2**). Since this protocol is considered best practice, clinicians at control sites will retain all control of their practice and be encouraged to follow this protocol even though the CDS will not be available to them.
3. Intervention sites will include strategies to increase use of the intervention by training clinicians on how to launch and use the CDS. Use of the intervention will be tracked with site-specific audit and feedback that is consistent with typical quality improvement initiatives at that site.

Given the ongoing and escalating opioid epidemic and wide scope of this trial, we anticipate that there may be concomitant interventions to stem OUD at study sites during the trial. We plan to permit these interventions as long as they are: (1) implemented before randomization so that they can be tracked and accounted for in the constrained randomization process, and (2) they are not a health IT intervention targeted at clinicians to initiate BUP in the ED.

Outcomes

The primary study hypothesis is that there will be higher rates of ED-initiated BUP with referral for ongoing MOUD with user-centered CDS compared with usual care. Therefore, the primary outcome will be BUP initiation in the ED, defined as whether or not an eligible patient is administered BUP in the ED and/or prescribed BUP upon discharge from the ED. Although this

is not a patient-centered outcome, it is a pragmatic and meaningful surrogate that will serve as a lead indicator of the CDS intervention's effect on engaging more OUD patients in treatment.

We will also evaluate the effect of user-centered CDS on the following secondary implementation outcomes as compared to usual care, informed by the RE-AIM framework:[42,43]

1. Referral to follow-up for ongoing MOUD treatment made in the EHR (patient-level; Y/N)
2. Prescription for naloxone at ED discharge (patient-level; Y/N)
3. Receipt of discharge instructions on opioid use, overdose education, naloxone education, and buprenorphine education (patient-level; Y/N)
4. Attending physician adoption rates (physician level):
   a. Provision of any ED-initiated BUP during the trial (Y/N)
   b. Provision of any referral for ongoing MOUD treatment during the trial (Y/N)
5. Receipt of Drug Addiction Treatment Act of 2000 training during trial (clinician level; Y/N)

Additional secondary implementation outcomes to be obtained from the web application include: clinician fidelity with the intervention assessed via a critical action checklist[44] and error rate of the intervention (using surrogates based on tool usage, e.g., application launched but not used, launching a page in the web application and spending less than two seconds on that page). The intervention will continue to be made available for use after the trial concludes; three months after trial completion, medical record review of eligible patients will be conducted at a subset of intervention sites to determine the maintenance rate of the intervention.

Sample Size

Current rates of BUP use in the ED range from 0-2% with most sites at 0%. Assuming a rate of BUP use in the usual care group of 1%, an increase to 10% would be a convincing and meaningful incremental effect of the intervention. Preliminary data from EDs that will be randomized in this trial suggest an Intraclass Correlation Coefficient (ICC) for BUP use of 0.01. The NIH group randomized sample size calculator[45] was used to determine the required number of sites to be randomized. With a two-sided type I error of 0.05, a conservative ICC of 0.03, and an expected average of 200 participants per site, a total of 12 sites will provide 90% power to detect a difference of 9%. This estimate is based on the assumption that all sites will have at least 200 unique patient visits during the trial that meet the EHR phenotype.

We estimated the impact of enrollment variability across sites on the required sample size using the formula described by Eldridge et al.[46] We added 2 sites to the total number of sites given the use of z-scores rather than t-scores in the estimation. As the coefficient of variation (CV) in the number of participants enrolled across sites increases, the required number of sites increases (**Figure 4**). To accommodate this potential variability, we will randomize a total of 20 sites (**Table 1**).

Table 1. Power to detect different effect sizes by coefficient of variation in enrollment given randomization of 20 sites.

	Effect Size (Difference in Proportions)					
Coefficient of Variation in Enrollment		0.05	0.06	0.07	0.08	0.09
	0	87%	94%	97%	99%	99%
	0.2	86%	93%	97%	99%	99%
	0.5	80%	89%	94%	97%	98%
	0.8	70%	80%	87%	92%	95%
	1.0	62%	72%	80%	87%	91%

Even with large variability in participant enrollment (CV=1), we will have over 90% power to detect a difference of 0.09. We will have good power (>80%) to detect effect sizes as low as 0.05 provided the variability in site enrollment is not great (<0.50).

Allocation

Study sites that meet readiness criteria at the time of randomization will be allocated 1:1 to CDS and usual care groups using constrained randomization conducted by personnel in the data coordinating center (DCC). The general method will follow procedures and recommendations from the literature on group randomized trials.[29]

With a small number of sites that differ in important ways, unconstrained randomization may not adequately balance important site characteristics. To improve comparability of treatment and control sites, personnel in the DCC under the direction of senior statistician (coauthor JDD) will list all possible allocations of treatment and control groups (with 20 sites, there are about

165,000 combinations of treatment and control groups). The imbalance score (□) from Raab and Butcher will be calculated for each possible allocation.[47]

$$\beta = \sum_{l=1}^{S} \omega_l (\overline{x}_{0l} - \overline{x}_{1l})^2$$

where *S* is the number of variables on which the groups should be balanced, ω_l is a weight calculated as the inverse variance of the mean of variable *l* across the hospitals, and the $\overline{x_l}$ represent the means of variable *l* across the hospitals in the intervention (indexed as 1) and control (indexed as 0) groups. A candidate set of 1000 possible allocations with the most favorable imbalance scores will be selected, and the final allocation will be selected at random from that candidate set.

Since clinicians must know how to launch and use the intervention, they will not be blinded to the allocation of their site as a control or intervention site. Clinicians may inform patients that they are using the CDS or not, as they deem appropriate consistent with CDS use in their usual practice. All study sites will post information in their ED informing patients of the study.

Data Collection

Outcome data will be collected via SQL query of the local EHR at regular intervals from data routinely collected in each hospital's EHR. This will facilitate large-scale data collection that would not otherwise be practical in an explanatory trial.

To enable consistent EHR data collection across sites, a master data dictionary of all data elements will be created. At each study site, the variables in the data dictionary will be validated against the institutional EHR to ensure that the variables are correctly mapped to the EHR field that corresponds to the clinical intent of the variable after accounting for documentation practices and workflow at each site.[48] For data quality assurance, the mapped variables will be validated against the EHR to ensure that the data are clinically relevant to the goals of the project and correctly represents the clinical data that clinicians use to make decisions. Additionally, data to determine compliance, use, and fidelity with the CDS intervention that could not be reliably abstracted from the EHR (e.g., DSM-5 OUD score, COWS score) will be abstracted from the web application's use logs. Information on whether the patient attended the referred follow-up visit and whether the patient was prescribed BUP as an outpatient will be abstracted from the EHR *only* if available in the same EHR (e.g., if the patient is seen for follow-up within the same system). Given the waiver of informed consent, we will be unable to track patients referred out-of-system.

Data will be sent from study sites to the study DCC at predetermined, regular intervals: initially every two weeks, but adjusted as needed. The DCC will conduct ongoing data monitoring activities on study data from all participating sites to ensure data received is what it is intended to be. Baseline data for the study participants will include demographic and clinical data such as age, gender, race, ethnicity, insurance status, past medical and psychiatric history, the most recent medical or psychiatric hospital admissions, recent enrollment in formal addiction treatment, active prescriptions for other opioids, and urine drug screen results as ascertained by regularly collected data in the EHR.

Data Management

Study data will only be available to members of the study DCC who are authorized for this study. To ensure the privacy and confidentiality of data for this project, DCC servers hosting data repositories are strongly firewalled; access to the repositories is permitted only through properly authenticated Web APIs. All data will be encrypted both at rest and in transit. The DCC database-hosting is certified by our institution's Information Security Office as conforming to HIPAA and our institution's data protection guidelines. All project computers are stored in locked offices within a building having limited, electronic passkey access. All computers are password protected and protected by our institution's firewall which is encrypted using Microsoft BitLocker. Individually identifiable or deducible data will only be by transmitted via secured telecommunications, never by unsecured telecommunications like email or electronic File Transfer Protocol (FTP). Procedures are in place for rapid recovery from hardware or database failure.

Data Monitoring

As a minimal risk implementation study of established best practices, an Independent Study Monitor will be utilized in place of a formal Data Safety Monitoring Board (DSMB). Interim monitoring will focus on adherence to the protocol, completeness of data retrieval from each ED's EHR, and uptake of the CDS intervention. A set of monitoring tables will be generated for this purpose. The Independent Study Monitor will report directly to the study DCC. No interim analyses for effectiveness are planned.

Study oversight

As a UG3/UH3 Demonstration Project, the NIH Health Care Systems Research Collaboratory and its Steering Committee core serve as the coordinating center and steering committee for this project and have given ongoing support to the design and rapid execution of this project. The DCC is composed of two biostatisticians, two clinical informaticists, a database manager, and two computer programmers. Study progress will be audited monthly for the first 3 months of the trial and then quarterly (but more frequently if needed) independent from investigators and the sponsor. Progress reports, including study progress and any Adverse Events, will be provided to the Independent Study Monitor following each of the monthly reviews. In terms of progress, auditing will focus on adherence to the protocol, completeness of data retrieval from each ED's EHR, and uptake of the CDS intervention. A set of monitoring tables will be generated by the DCC for this purpose.

Analysis Plan

General Considerations: This is a cluster randomized trial to test the hypothesis that there will be higher rates of provision of ED-initiated BUP and referral for ongoing MOUD with user-centered CDS compared with usual care. Analyses will be conducted as intention to treat including all individuals regardless of intervention receipt. While the unit of randomization is at the level of the ED, the unit of analysis will be the patient. Analyses of primary and secondary outcomes will be conducted using logistic regression with weighted generalized estimating equations (GEE) to account for clustering from the EDs and physicians in patient outcome models.[49] Analyses will be performed in SAS v9.4 (Cary, NC) with a two-sided type I error of 0.05 (unless otherwise specified). For the primary and secondary analyses described below, only the first ED encounter for an individual patient will be used. Supportive analyses will include patients with repeated ED visits.

Comparability of Baseline and Intervention Site Patients: Distributions of baseline demographic and clinical characteristics will be described during baseline and intervention periods. Comparability for continuous variables will be examined graphically and by summary statistics (means, medians, quartiles, etc.). Categorical variables will be examined by calculating frequency distributions.

Analysis of Primary Outcome: The primary outcome, initiation of BUP in the ED, will be assessed for all patients that meet the criteria for the EHR phenotype. Intervention differences (CDS vs usual care) for this dichotomous outcome will be examined using weighted GEE. The

weighted GEE provides consistent parameter estimates when the dropout mechanism is correctly classified by implementing the inverse-probability weighted method to account for dropouts under the missing at random (MAR) assumption. Inverse probability weights are estimated by a logistic regression of dropout. The weighted GEE model will contain an effect for intervention (CDS vs usual care). An exchangeable working correlation will be used to account for clustering of responses within ED and physicians. The model will also include cluster-level covariates included in the constrained randomization and patient-level covariates that may be associated with the delivery of BUP (age, gender, race, ethnicity, insurance status, past medical and psychiatric history, recent medical or psychiatric hospital admissions, recent enrollment in formal addiction treatment, active prescriptions for other opioids, and urine drug screen results). Linear contrasts will be used to estimate treatment differences along with 95% confidence intervals in the proportions of ED patients that received BUP in CDS vs. usual care. Given the relative advantages of Generalized Estimating Equations, and generalized linear mixed models (GLMM) sensitivity analyses will compare treatments using a logistic regression with GLMM, with random effects for ED and physician.

Analysis of Secondary Outcomes: Secondary outcomes such as referral for MOUD appointment, attendance at an MOUD appointment (if available in the EHR), prescription for naloxone at ED discharge and receipt of discharge instructions will be evaluated using weighted weighted GEE as described above. Assessments of the physician including provision of any ED-initiated BUP during the trial, provision of any referral for ongoing MOUD treatment during the trial and receipt of Drug Addiction Treatment Act of 2000 training during the trial will be compared between CDS and usual care using GEE. These models will be stratified by the number of eligible patients the physician encountered during the trial and will include an effect for intervention, cluster-level covariates included in the constrained randomization, and an exchangeable working correlation. Discrete numeric outcomes such as clinical fidelity will be compared using the GEE with a log link and a negative binomial distribution.

Plan for Missing Data: Several strategies will be imposed to accommodate the likelihood that missing data will occur during this study. Prevention is the most obvious and effective manner to control bias and loss of power from missing data.[50] As noted in the Data Collection section above, prior to the trial we will pilot data collection procedures. Variables with large proportions of missing will be excluded from collection. We will follow the intent to treat principle, requiring follow-up of all EDs randomized regardless of the treatment received.[51] Regular data retrieval

from EHRs combined with monitoring and missing data reports will trigger protocols for tracking and obtaining missing data. Despite these prevention efforts it is reasonable to assume missing data will occur. Our primary analysis is valid under the assumption that missing data will be missing at random (MAR).[52] We will evaluate the plausibility of this assumption by determining the extent of missing data and use logistic regression to identify factors associated with missing data. As appropriate, we will conduct sensitivity analysis using pattern-mixture and selection models under missing not at random (MNAR) assumptions to examine the robustness of conclusions of the primary analysis to missing data.[50,52]

Patient and Public Involvement

The development of the research question and outcome measures was led by emergency physicians, the primary population being studied. Formal user design sessions were conducted with both attending and resident physicians to ensure the CDS would be useful and would not interfere with patient care nor pose an undue burden on clinicians' time. The results of the study will be shared with the clinicians at participating sites via a broadcast email notification of publications. Patients did not participate in the design of the study and will not be involved in recruitment and conduct of the study.

ETHICS AND DISSEMINATION

We plan to obtain all necessary regulatory and human subjects protection approvals and procedures. The protocol has been approved by the Western Institutional Review Board, central IRB (protocol number 20182278, study number 1189765). Any important protocol modifications will be submitted to Western Institutional Review Board as protocol amendments. The local IRBs at each participating site will implement a reliance agreement with this central board. We anticipate a waiver of informed consent under the Common Rule (45 code of federal regulations (CFR) 46.116 given that:[53,54] (1) the research involves no more than minimal risk to the subjects;[55] (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) subjects will be provided with additional pertinent information after participation.

Patients are not considered human subjects by HHS regulation 45 CFR 46.102(f)[54] since: (1) no identifiable private information will be collected, (2) the intervention does not target the patient, and (3) EHR data will be collected retrospectively without interaction with the patient.

Therefore, consent is not applicable to this population. Furthermore, all recommendations included in the CDS intervention are considered best practices in treatment of OUD. The OUD population has a high underlying risk of morbidity/mortality (approximately 5% risk of death in 12 months).[8] Patient rights and welfare will be protected per standard practice. Therefore, the risk to a patient with OUD who is not receiving MOUD treatment in their ordinary daily lives greatly exceeds the risk of the EMBED intervention. All study sites will post details about the study in a location visible to patients to make them aware of the option to receive BUP and referral to treatment so as best to offer an informed decision for requesting care. Patients will retain the right to request MOUD treatment at any study site.

Clinicians at all study sites will have access to all standard OUD medications and services to which they would otherwise have access to treat OUD patients. Clinicians will retain all control of their practice and at intervention sites have the option whether or not to use the intervention (i.e., can opt out). Clinician identifiers will be collected in order to follow practice patterns. However, the investigators will be blinded to both site and clinician identifiers. Each system will use an Honest Broker to protect the welfare and identity of each site and clinician and allow adjudication for analyses. Clinicians will be made aware of the study, its outcomes, the data to be collected and, at intervention sites, how to use and opt out of using the CDS via broadcast e-mail and direct communication by site champions. A flow diagram of the study's clinical protocol (**Figure 2**) will shared with clinicians and posted in the clinical work area of all study sites. Since this protocol is considered best practice, clinicians at control sites will retain all control of their practice and be encouraged to follow this protocol even though the CDS will not be available to them. As this is a pragmatic trial focused on implementing this intervention in a way that is as close to routine care as possible, consenting clinicians would not be consistent with routine CDS implementation and could jeopardize the scientific validity of the CDS intervention to overcome barriers to adoption of this practice[53]. Given the stigma[11] associated with treating individuals with OUD, the additional burden of the consent process could be a deterrent for clinicians to provide MOUD treatment to appropriate patients and bias the sample to clinicians with less stigma toward treating these patients. For this reason and since clinician data will be de-identified and unavailable to the investigators, we propose a waiver of consent of the clinicians to ensure the scientific validity of our findings. There is precedent for such a waiver in a similar situation.[56]

Results will be published in open-access, peer-reviewed journals, presented at national meetings, and shared with the clinicians at participating sites via a broadcast email notification of publications. The full protocol will be published for public access; access to the participant-level dataset will be made in accordance with NIH policy after safeguarding that the datasets are fully de-identified at the site, provider, and patient level. No professional writers will be used. Authorship eligibility will follow the guidelines of the International Committee of Medical Journal Editors.[57]

Figure Legends

Figure 1. Schematic diagram of parallel, cluster-randomized study design.

Figure 2. Clinical algorithm for ED-initiation of buprenorphine.

Figure 3. Graphical user interface of the user-centered CDS EMBED intervention

Figure 4. Number of study sites required as a function of coefficient of variation for site size assuming an ICC of 0.03

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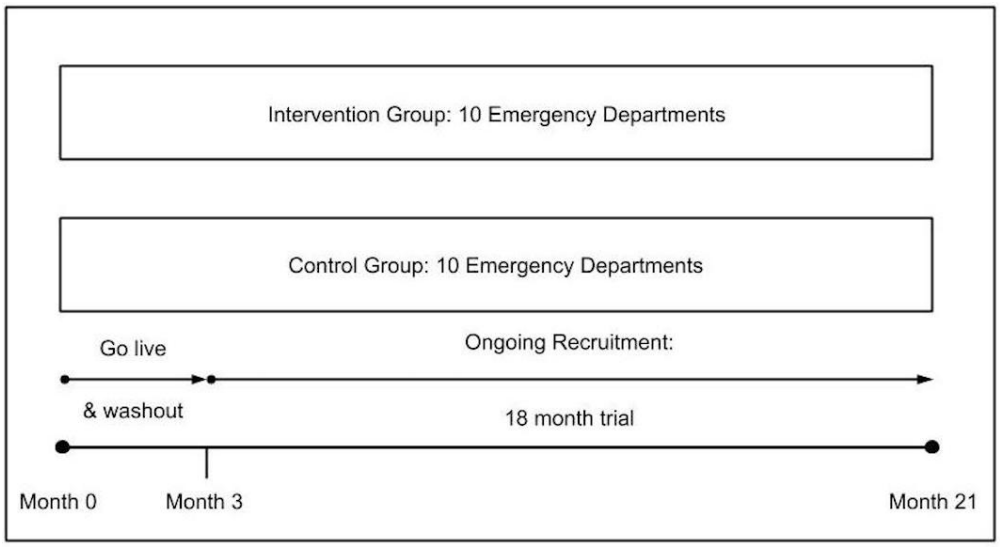

Figure 1. Schematic diagram of parallel, cluster-randomized study design

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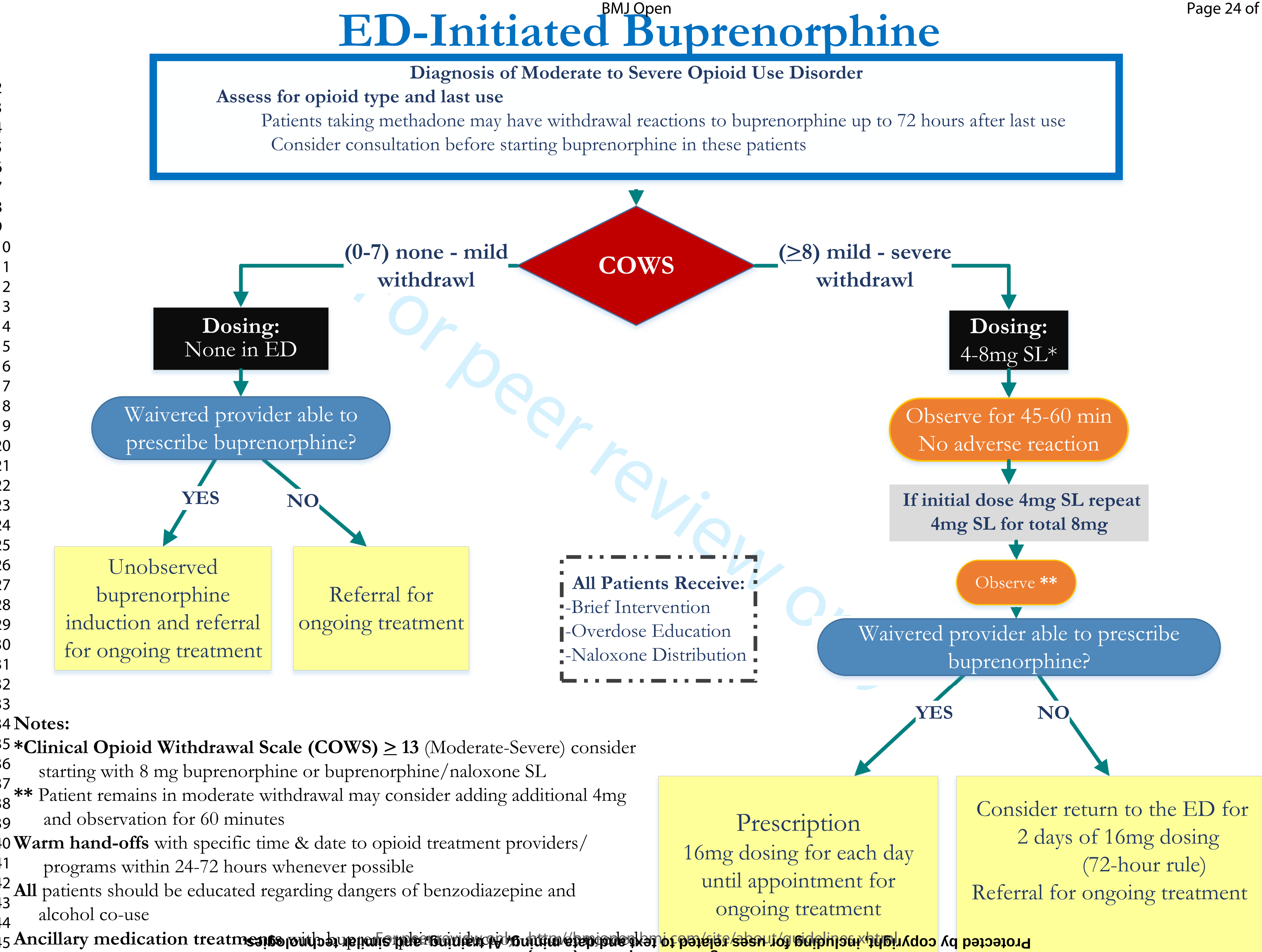

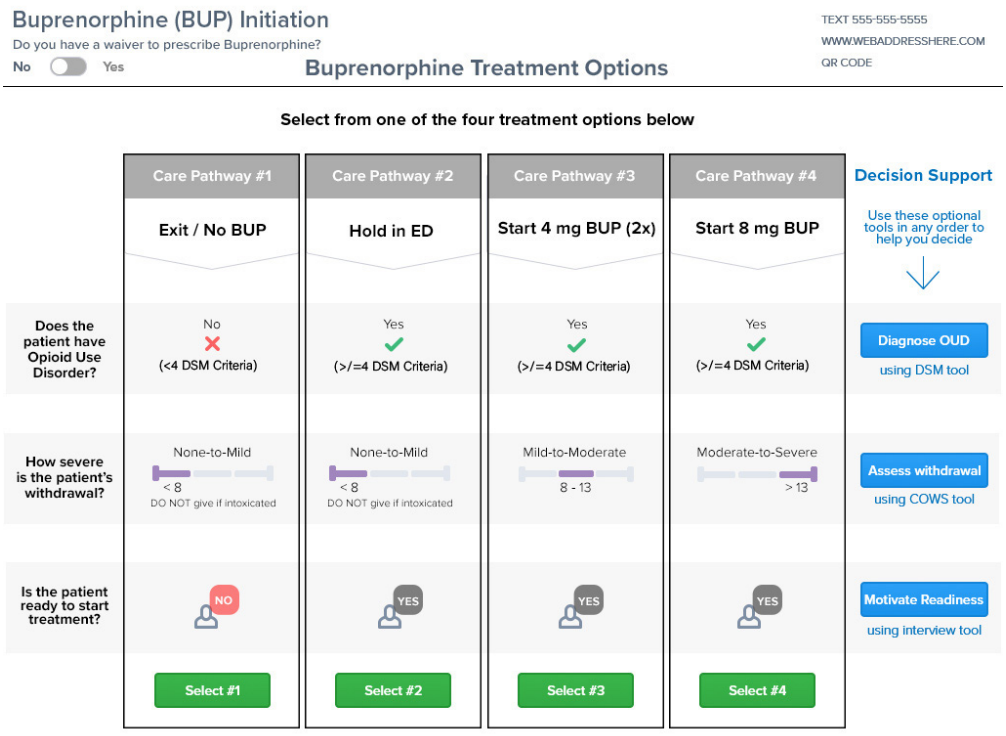

Figure 3. Graphical user interface of the user-centered CDS EMBED intervention

86x65mm (300 x 300 DPI)

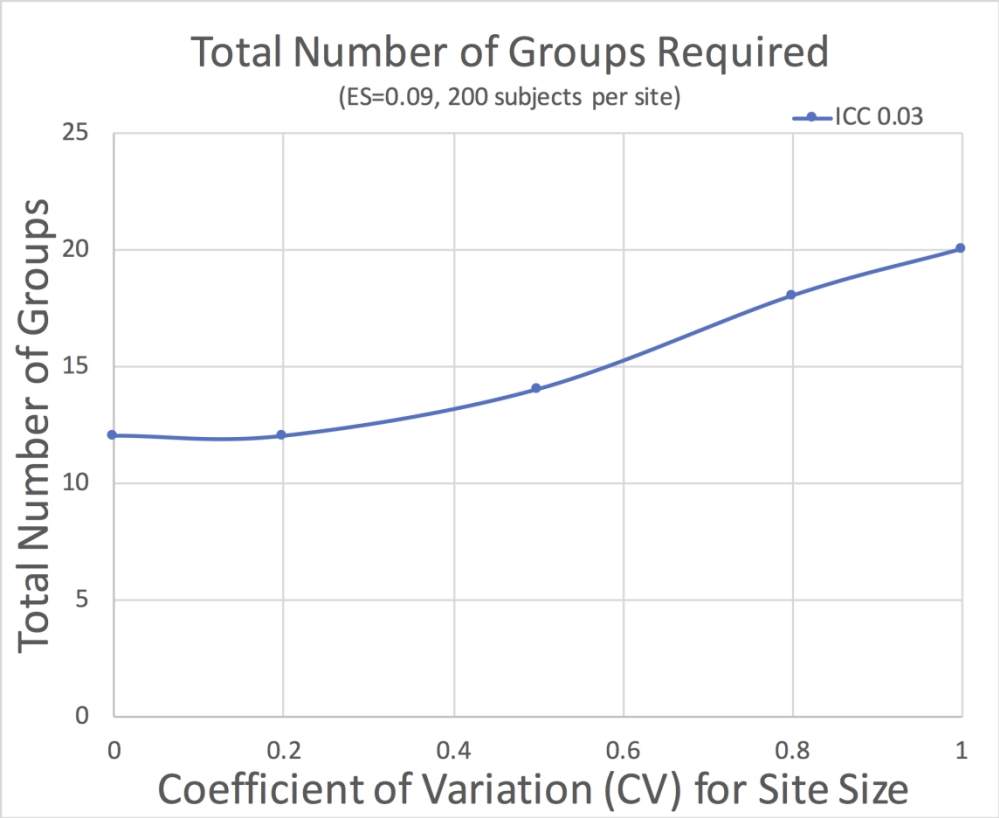

Figure 4. Number of study sites required as a function of coefficient of variation for site size assuming an ICC of 0.03

181x148mm (300 x 300 DPI)

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	13
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	N/A
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	N/A
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether analysis was by original assigned groups	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	N/A
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	N/A
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	1
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	N/A
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	11
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	N/A
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	11

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Page 1 (title page)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry Page 2 (abstract)
	2b	All items from the World Health Organization Trial Registration Data Set Clinicaltrials.gov is compliant with the WHO Trial Registration Data requirements
Protocol version	3	Date and version identifier Page 1 (Title page)
Funding	4	Sources and types of financial, material, and other support Page 1 (Title page)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Page 1 (Title page)
	5b	Name and contact information for the trial sponsor Page 1 (Title page)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities Page 1 (Title Page)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) p 13

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention pp 4-5
	6b	Explanation for choice of comparators page 5
Objectives	7	Specific objectives or hypotheses: page 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) pp 5-6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained page 6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) pp 6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered pp 7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) p 16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) N/A: as a pragmatic trial, participant adherence to intervention protocol is not a goal; we will observe participants using the CDS as they choose
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial p. 8

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended pp 8-9 and 13-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations Table 1
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size N/A: Sites have already been recruited
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions pp 10-11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned N/A: allocation will not be concealed
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions pp 10-11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how p 11, 16

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial N/A
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol pp. 11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols N/A; follow-up is complete on the date of the study encounter
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol p 12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol pp 13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) pp 13-14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) pp 13-14
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed p 12

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct p. 16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor p. 13
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval Abstract
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) p. 15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) N/A see pp 15-16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial p 16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site pg 1 (Title page)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators p12

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions pp 15-16
	31b	Authorship eligibility guidelines and any intended use of professional writers p 16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code p 16
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.