NIH Collaboratory Rethinking Clinical Trials®

Health Care Systems Research Collaboratory

Regulatory/Ethics Consultation Call:

Pragmatic Trial of User-Centered Clinical Decision Support to Implement Emergency Department-Initiated Buprenorphine for Opioid Use Disorder (EMBED)

Initial Call: Thursday, July 12, 2018

Meeting Participants

Cynthia Brandt (Yale University), Judith Carrithers (Advarra), Gail D'Onofrio (Yale University; Co-Principal Investigator), Sarah Duffy (NIH), Kristen Huntley (NIDA), Jonathan McCall (Duke), Shara Martel (Yale University), Marijo Mencini (Duke), Ted Melnick (Yale University; Co-Principal Investigator), Catherine Meyers (NIH), Tammy Reece (Duke), Jeremy Sugarman (Johns Hopkins)

Follow-up Call: Monday, August 6, 2018

Meeting Participants

Laura Bankowski (Yale), Judith Carrithers (Advarra), Sarah Duffy (NIH), Kristen Huntley (NIDA), Molly Jeffery (Mayo), Jonathan McCall (Duke), Marijo Mencini (Duke), Ted Melnick (Yale University; Co-Principal Investigator), Mehul Patel (UNC), Tammy Reece (Duke), Jeremy Sugarman (Johns Hopkins), Wendy Weber (NIH), Dave Wendler (NIH), Liz Wing (Duke)

AGENDA ITEMS	DISCUSSION	ACTION ITEMS
Review of Demonstration Project	• Study Co-Principal Investigator Ted Melnick (Yale University) provided a summary description of the EMBED pragmatic clinical trial (UG3 pilot phase). The goal of EMBED is to implement and evaluate a user-centered clinical decision support (CDS) tool that facilitates the use of buprenorphine/naloxone therapy (BUP) for opioid use disorder (OUD) initiated in emergency department settings. The intervention consists of electronic treatment guidance for the physician and is designed to be embedded within existing workflows. • **Collaborative network partners:** o Yale University o Mayo Clinic o University of North Carolina at Chapel Hill o Cooper University Hospital • **NIH Institute:** National Institute on Drug Abuse (NIDA)	

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	• **Study design:** EMBED was originally designed as a stepped-wedge study, but has recently been changed to a parallel, constrained group-randomized design. Randomization will occur by site and will be standard of care vs. intervention. EHR phenotyping will be used to identify patients passively. Data collected will primarily be EHR data from the site, with additional data linked from outpatient referral centers (e.g., addiction treatment centers). o **Primary outcome:** The rate of BUP treatment initiated in the ED (Emergency Department) o **Secondary outcome:** The rate of referral for continuing OUD treatment • Clinicians are the study participants in terms of the intervention; patients identified by EHR phenotyping are evaluated retrospectively. • Data from the clinical EHR will include protected health information (PHI), but the research data environment will use unique identifiers with no PHI. o The only ongoing data capture about continued substance use will be that which is documented in the EHR. o Study is designed as a retrospective review of deidentified data by the study team weeks after the ED encounter. • The design of the intervention is part of the UG3 phase and is being programmed.	
Status of IRB approval	• Western IRB (WIRB) will be the IRB of record. Submission to the IRB is expected to occur within 1 week.	
Risk classification	• The investigators consider EMBED to be minimal risk. Although the background mortality for patients with OUD is high, initiation of treatment is known to be beneficial, and incorporating it in the ED setting in streamlined fashion is likely to be beneficial. The likely greatest risk from the study relates to patient privacy, but safeguards will be in place (see discussion below). • The clinical intervention (BUP) is evidence-based, but there is equipoise related to whether an information technology (IT)-based intervention can be integrated in a way that allows its successful implementation in the ED.	Completed: Per the 7/12/18 discussion, the Collaboratory coordinating center provided the study team with information about the use of other opt-out

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	• Risks related to privacy are difficult to assess until the actual mechanics of data exchange and storage are worked out. However, to help ensure privacy and confidentiality of data for this project, the study team will store and use identifiable data in a Yale University Information Technology Services (ITS) hosted environment that is approved by its Security Office. The physical location of the facility is limited to ITS, and server access is limited only to those who are authorized. All personnel who have access to the data must have passed appropriate HIPAA training coursework. • Potential risks to patients, especially those that might result from privacy breaches, need to be broadly considered. The acquisition of data and its linkage with other data will be important, and measures being taken to de-identify data will need to be clear. OUD patient data will not be collected. Clinician and site identifiers will be collected and de-identified by an Honest Broker at each health system. • Clinicians will retain complete control over treatment decisions and have the option whether or not to use the intervention. The patient retains the right to refuse treatment or request treatment at any time.	procedures in pragmatic clinical trials.
Consent	• It is expected that clinicians, and not patients, are considered to be EMBED study subjects. The intervention is focused entirely on clinician behavior and whether their use of the tool increases the rate they initiate BUP and refer for ongoing treatment. The EMBED study team will seek a waiver of informed consent for clinicians for data collection during the UG3 phase. • Four criteria that must be present for consent to be waived:[1] o The study is minimal risk o The study is impracticable without waiver of consent o The study does not adversely affect patients' rights/welfare o Where appropriate, study subjects will be provided with additional information about their participation	• Completed: The study team revised their supplemental material providing additional information about the protocol and plans for handling data/protecting patient privacy. • Completed: Per the 8/6/18 discussion, the coordinating center has provided the study team with the OHRP

[1] 45 CFR 46.116

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	• Clinician identifiers will be collected in order to follow practice patterns, but the investigators will be blinded to both site and clinician identifiers. Each system will use an Honest Broker to protect not only privacy but also the welfare and identity of each site and clinician and allow adjudication for analyses. • Similarly, all clinicians will have access to all standard OUD medications and services to which they would otherwise have access to treat OUD patients. Clinicians retain all control of their practice thereby not adversely affecting their rights or welfare. • The investigators believe it would be impractical to request consent from each clinician. It would be a deterrent for clinicians to participate in this intervention with the added complications of consent. • If the study meets all criteria for waiving consent, there are multiple options for informing participants. If not, the default assumption is that written consent will be required. Given the nature of the intervention and population, the study team will consider providing some form of notification, such as broadcast or poster, at control and intervention ED sites.	guidance on coded private information use in research.
Privacy/HIPAA	• All output containing individually identifiable information is treated as confidential data. This information is never transferred electronically via email or other protocols. Shredders are used on any printed material containing individual identifiers. • All personnel who have access to the data must complete and pass appropriate HIPAA training coursework.	
Monitoring and oversight	• A traditional data monitoring committee is not envisioned for this study; however, an advisory/oversight panel of IT experts will oversee the study; this approach has been approved by the IC. • Data may be harvested in periodic fashion, but that is not yet certain. It was noted that summary statistics about site enrollment are regularly reported (per requirements) to the coordinating center and to NIH. The frequency of reporting can be variable, however.	
Issues beyond the study	• A certificate of confidentiality will be automatically provided per new NIH policy. This certificate adds provisions for future research uses and confidentiality obligations for future data sharing.	Completed: Per the 7/12/18 discussion, the coordinating center

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		provided copies of previous ethics minutes from the ABATE (PI: Huang) and ICD PIECES (PI: Vazquez) studies for reference – the former because it was also a health system-level intervention; the latter because of similarities in nature and scope.
Items for resolution	• In the follow-up call, the investigators provided answers to the items below, summarized here (further details are in the attached supplemental material): o It would be useful to circulate the current version of the protocol that incorporates the change to the study design (from stepped-wedge to a constrained parallel group randomization). A detailed protocol will be distributed. o How are data protections articulated in the study protocol, and what are the implications for those measures with regard to meeting criteria for a determination of minimal risk? The electronic data files for this study will be processed on the dedicated, layered-security system, which can be accessed only by the Yale Data Coordinating Center and designated project staff that are under the direct supervision of the PI. Since the system is behind multiple firewalls, is monitored regularly, and is accessible only to key personnel, the risk of unlawful penetration is not a significant data safeguard concern. (See supplement.) o If a waiver of consent is sought for the study, how would that comport with the 4 criteria noted above? The investigators believe that a waiver of consent for the clinician-participants comports with the 4 regulatory criteria (see attachment). o Is there a plan in place to provide notification/study findings to study participants after the project concludes? Clinicians will be made aware of study findings by use of a broadcast e-mail to all participating sites referencing the ClinicalTrials.gov record as	

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	well as notification of publications to open-access journals and articles attributable to the study, in which results of the study will be disseminated. o Will consent issues/determinations apply to both patients and physicians? They will apply only to physicians as the human subjects of this trial. o Will general notification, opt-out, broad notification, or oral consent be used? The clinicians from both the intervention and control groups will be made aware of the use of the intervention and the outcomes to be explored during this trial. The clinicians, by way of broadcasts and site champions will be made aware of the opt-out option as well as instructed on how to opt out. o With regard to privacy issues (and waiver of HIPAA authorization): will it be possible link patient data to data in the research record? OUD patient data will not be collected. The Honest Broker in each system could in theory, link to patient data using a Contact Serial Number (CSN), generated by the EHR system, which is not protected health information (PHI) and requires special administrative access to the local EHR. o Are there any plans to share data, and do those create any ethical or regulatory issues? The Yale School of Medicine is and will remain HIPAA compliant, and therefore any datasets resulting from human participant research will be free of any identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of individual subjects. Furthermore, in accordance with HCS Research Collaboratory program requirements, data will be shared in a timely manner (upon publication) with appropriate privacy and confidentiality protections, in accordance with the Data Sharing Policy developed by the HCS Research Collaboratory Steering Committee. o Are there any questions about whether the considerations in the certificate of confidentiality will apply to this study? Plans are in place to protect confidentiality of all participants and all identifying characteristics will be de-identified.	

(8/7/18 post-call) RESPONSES FOR ETHICS & REGULATORY CORE

1. ***Ethics & Regulatory Core:*** *It would be useful to circulate the current version of the protocol that incorporates the change to the study design (from stepped-wedge to a constrained parallel group randomization*

Response:

The study design is a pragmatic group randomized trial carried out in approximately 20 emergency departments (ED) across approximately six healthcare systems over 18 months. The intervention will consist of a user-centered clinical decision support (CDS) system available for physician use to 1) determine whether patients presenting to the ED meet criteria for opioid use disorder (OUD), 2) assess withdrawal symptoms, and 3) ascertain patient willingness to initiative buprenorphine (BUP) for treatment of OUD. The CDS guides the ED clinician to initiate medication for OUD treatment and to facilitate follow up as deemed clinically appropriate. The primary outcome is the rate of BUP initiated in the ED (either as administration of BUP in the ED and/or prescription of BUP upon ED discharge). Secondary outcomes are 1) rates of receiving a referral appointment for addiction treatment, 2) clinician fidelity with the user-centered CDS using a critical action checklist, 3) rates of clinicians providing ED-initiated BUP, 4) rates of clinicians providing referral for ongoing medication for OUD, and 5) rates of clinicians who have received Drug Addiction Act of 2000 training. Data will be collected pragmatically from the EHR and the CDS web application. Additional details of the methods and analysis plan are available in a detailed protocol that will be distributed after this call.

2. ***Ethics & Regulatory Core:*** *How are data protections articulated in the study protocol, and what are the implications for those measures with regard to meeting criteria for a determination of minimal risk?*

Response:

Study data will only be available to members of the Yale Data Coordinating Center who are authorized for this study. To ensure the privacy and confidentiality of data for this project, we will store and use identifiable data in a Yale University ITS hosted environment that is approved by Yale ITS Information Security Office. The physical address to the facility is limited to ITS, and server access is limited only to those who are authorized. All personnel who have access to the data will pass appropriate HIPAA training coursework. The main levels of security are:

- Physical media that are received from the distributer or any physical copies of the data will be encrypted while at rest and will be held in a locked, fireproof cabinet within the office of Dr. Melnick.
- Project computers are all password protected, are protected by the Yale University firewall, are encrypted using Microsoft BitLocker, and are in locked offices within a building having limited, electronic passkey access.
- All servers and workstations have been certified by Yale's Information Security Officer as compliant with Yale's HIPAA policy (http://hipaa.yale.edu/).

- All computing devices follow Yale's password policy, which requires strong passwords with periodic mandatory changes.
- All computers are on the Yale internal network which is maintained and monitored by Yale ITS. The servers on the Yale internal network have no direct connection to the external network without special setup by Yale ITS after serious security screening performed by the Yale Information Security Office.
- The PHI database will reside on the local network and will be accessible only by selected data project staff.
- All servers employ redundant drives to protect against data loss in the event of hardware failure. All databases are backed up by Yale ITS and can be recovered in the event of database corruption.
- All servers, including the PHI server, are located in a secure, environmentally-controlled facility. Electrical power to this facility is protected by a standby power system maintained by Yale Facilities. This system includes generators to protect against complete building shutdowns.
- Files used for analysis are required to reside on servers and are never stored on desktop computers.
- All staff requiring access to PHI must complete HIPAA training provided by Yale University, and must additionally follow procedures for the protection of electronic and printed data.

The electronic data files for this study will be processed on this dedicated, layered-security system, which can be accessed only by the Yale Data Coordinating Center and designated project staff that are under the direct supervision of the PI. Since the system is behind multiple firewalls, is monitored regularly, and is accessible only to key personnel, the risk of unlawful penetration is not a significant data safeguard concern.

Individually identifiable or deducible data will not be transmitted by unsecured telecommunications, which include the Internet, email, and electronic File Transfer Protocol (FTP).

At the conclusion of this study, we will follow the NIH's data retention guideline.

Lastly, all output containing individual identifiable information is treated as confidential data. This information is never transferred electronically via email or other protocols. Shredders are used on any printed material containing individual identifiers.

3. In reference to the *Ethics & Regulatory Core* concerns of how a waiver of consent request would comport with the 4 criteria Assessment of risk waiver of consent, we have considered the following as outlined in numbers 3.1 – 3.4. Additional Core questions are addressed below 3.1- 3.4.

We anticipate a waiver of informed consent for clinicians will be obtained for data collection during the UH3 phase.

NOTE: There are no patient outcomes being collected. The most important aspects of EMBED is testing whether CDS built for users' needs increases that rate at which clinicians

offer BUP initiation and referral for ongoing treatment. The test of the effect of BUP in the ED on patient outcomes has already been performed.

3.1. The research involves no more than minimal risk to subjects (Clinicians)

OUD Patients: Information and identifiers from patients will **not** be collected, as this is a trial for clinician use of the Clinical Decision Support (CDS) for opioid use disorder (OUD). Clinicians will retain complete control over treatment decisions and at intervention sites have the option whether or not to use the intervention. The patient retains the right to refuse treatment or request treatment at any time. All tools included in the CDS are validated clinical tools that are part of recommended best practices. The OUD population has a high underlying risk of morbidity/mortality (approximately 5% risk of death in 12 months per LaRochelle Annals of IM 2018). The risk to a patient with OUD who is not receiving medication for opioid use disorder in their ordinary daily lives greatly exceeds the risk of the EMBED intervention.

Clinicians: Clinicians in the control group will have access to all standard OUD medications and services to which they would otherwise have access to treat OUD patients. Clinicians retain all control of their practice. The intervention group will receive interventions which are already accepted as best practices; none of the proposed interventions are experimental, and they do not carry any risks beyond what is expected in standard medical care. 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.

3.2. The waiver or alteration will not adversely affect the rights and welfare of subjects (Clinicians)

OUD Patients: the unit of randomization for EMBED is the hospital and the unit of analysis is clinician practice regarding treatment of patient suspected to have OUD. As there will be no identifiable private information collected from OUD patients, and no data received through direct intervention/ interaction with the OUD patients, we believe that this trial would be considered non-human subjects for this population, thereby making consent not applicable. All patient data will come from the EHR and be de-identified with a unique study ID assigned at the time of data collection. The study ID will be assigned in such a way that it will not be traceable to the subject other than by means of an honest broker who holds the key to break the code. The data will be reviewed in a manner consistent with a retrospective chart review in that the ED notes will be available for data review and be reviewed days after the OUD patient has presented to the ED. If the data collection is limited to patient information taken from the EHR, minimal risk to the OUD patients would be maintained by deidentifying patient information before transmission to the DCC and not attempting to link later patient activity like showing up to MOUD follow-up. Patient rights and welfare will be protected per standard practice. OUD patients have the right to refuse MAT or a referral to treatment in the same way they can refuse any medication or referral. 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.

Clinicians: clinicians have the option of not using the CDS intervention (can opt out). The clinicians from both the intervention and control groups will be made aware of the use of the intervention and the outcomes to be explored during this trial, as well as the data being collected for use in this trial. The clinicians, by way of broadcasts and site Champions will be made aware of the opt out option as well as instructed on how to opt out. In an effort to promote transparency, a flow diagram of the study's clinical protocol will be sent to clinicians by broadcast e-mail and posted in the clinical work area. 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.

Clinician and site identifiers will be collected and de-identified by an Honest Broker at each health system.

3.3. PRACTICABILITY: The research could not be carried out without the waiver or alteration

From McKinney article: Practicability can be looked at from three perspectives.

I. *Scientific Feasibility: Can the scientific question be answered if research participants are aware of the experiment's purpose?*

EMBED

a. OUD patients: patients will not be made aware as the intervention as this is evidence-based practice that should be routine care for patients with OUD.

b. Clinicians: Clinicians will be made aware of the CDS in the same way they would be notified about any CDS in the EHR.

II. *Logistical feasibility: for example, obtaining consent from each individual would be extremely difficult in some large studies of a minor Intervention (e.g. one that examined whether the rate of false-positive results from blood cultures is decreased more by the use of alcohol or betadine to clean the skin prior to sampling).*

EMBED

a. OUD patients: Being as patient identifiers will not be collected, this would not be applicable. If obtaining consent from OUD patients without collecting identifiers would be required, this would be impractical being as this Pragmatic Trial is concentrated on helping the clinicians integrate this intervention in a way that is as true to usual care as possible. The process of consenting each OUD patient would be an unnecessary burden to the clinicians in their ED practice thereby likely decreasing their willingness to adopt this evidence-based practice and/or discourage participation in the trial. Additionally, as there will be no identifiable personal health information collected from OUD patients, and no data received through direct intervention/ interaction with the OUD patients, we believe that this trial would be considered non-human subjects for this population, thereby making consent not applicable.

b. Clinicians: As this is a Pragmatic Trial focused on implementing this intervention in a way that is as close to routine care as possible, it would be impractical to request consent from each clinician. We will be applying for a waiver of consent for this population. It would be a deterrent for clinicians to participate in this intervention with the added complications of consent.

III. *Concerns situations in which it is feasible to obtain individual prospective consent but at the expense of scientific validity (by introducing bias) and/or in terms of the resources required.*

EMBED

a. OUD patients: patient identifiers will not be collected, this is not applicable.

b. Clinicians: Clinician stigma to treating individuals with OUD could bias the sample if clinicians that have a stronger stigma toward these patients can refuse to participate. 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 the CDS intervention to overcome barriers to adoption of this practice. There is precedent for such a waiver in a similar situation, Suffoletto et al. The Effect of a Statewide Mandatory Prescription Drug Monitoring Program on Opioid Prescribing by Emergency Medicine Providers Across 15 Hospitals in a Single Health System. *J Pain. 2018;19(4):430-8.*

3.4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation

***Ethics & Regulatory Core**: Is there a plan in place to provide notification/study findings to study participants after the project concludes?*

Response:

OUD patients: As OUD patient data will not be used, there will be no findings that would be reportable to this population. In an effort of good faith, we will incorporate a broadcast system in the ED with approved IRB text to be used locally at each site as they see fit (i.e., posters, screen savers, information sheets).

Clinicians: Clinicians will be made aware of study findings by use of a broadcast e-mail to all participating sites referencing the ClinicalTrials.gov record as well as notification of publications to open-access journals and articles attributable to the study, in which results of the study will be disseminated.

Additional Ethics & Regulatory Core Concerns

Ethics & Regulatory Core: *Will consent issues/determinations apply to both patients and physicians?*

Response:

No, consent will only apply to clinicians/ physicians, identifiers will not be collected for OUD patients and therefore will not need to be consented.

Ethics & Regulatory Core: *Will general notification, opt-out, broad notification, or oral consent be used?*

Response:

OUD patients: consent will not be applicable for OUD patients as identifiers will not be collected. They will receive standard care.

Clinicians: Opt out and broadcast notification will be used. Clinicians will be informed of the research by broadcast. Posters targeting the clinicians with information about the study will be posted in all participating emergency departments. Additionally, the participating health systems will receive broadcast e-mails detailing the trial and the outcomes being studied as well as an explanation of the option and process to Opt out. That is, even though randomization is by site, clinicians at each site can opt out of using the intervention. Further, Clinical Champions identified at each site will discuss the intervention in the same way they would discuss any CDS being implemented in their EHR locally.

Ethics & Regulatory Core: *with regards to privacy issues (and waiver of HIPAA authorization): will it be possible to link patient data to data in the research record?*

Response:

OUD patients: OUD patient data will not be collected. Patients will instead be identified with a unique study identifier that The Honest Broker in each system could in theory, link to patient data. Identifiers may be system-dependent, but it will be mandatory that the identifier which is used is not an identifiable piece of protected health information (PHI) and that special administrative access is required to the local EHR to use this identifier to link back to patient data. Further, we will not be collecting or considering the actual date of OUD patient visit, but rather, we will collect the day on which the OUD patient visited (i.e. Day 42 of the trial) without knowing the exact start date for each site. As such, we would not be able to link a visit day with a OUD patient.

Clinicians: We intend to integrate the use of an Honest Broker for each health system to de-identify the specific sites in which this trial is taking place and data is being collected. The Honest Broker for each external health system will remove all identifiers and be responsible for the key to the identifiers.

Ethics & Regulatory Core: *Are there any plans to share data, and do those create any ethical or regulatory issues?*

Response:

In addition to complying with the below plan as outlined in the original grant application, all external sites will be required to provide a data use agreement which will be subject to their specific institutions' research office and local governance review.

Grant application data sharing plan:

We are committed to the sharing of final research data, being mindful that the rights and privacy of people who participate in research must be protected at all times, and that restrictions on data sharing may be imposed by agreements with third parties. The Yale School of Medicine is and will remain HIPAA compliant, and therefore any datasets resulting from human participant research will be free of any identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of individual subjects. Furthermore, in accordance with HCS Research Collaboratory program requirements, data will be shared in a timely manner (upon publication) with appropriate privacy and confidentiality protections, in accordance with the Data Sharing Policy developed by the HCS Research Collaboratory Steering Committee (https://www.nihcollaboratory.org/Pages/KnowledgeRepositoryTabs.aspx?Paged=TRUE&p_SortBehavior=0&p_Created=20140715%2016%3a32%3a51&p_ID=71&PageFirstRow=61&&View={F028E1AA-0D11-4E13-BC09-CE77694521B8}). Similarly, data generated during the course of this study will be made publicly available upon publication for analysis by the scientific community by posting it on a website. Sharing of data generated by this project is an essential part of our proposed activities and will be carried out in several different ways. We want to make our results available to academic community to promote improved patient care, and avoid unintentional duplication of research. Conversely, we would welcome collaboration with others.

Ethics & Regulatory Core: *Are there any questions about whether the considerations in the certificate of confidentiality will apply to this study?*

Response:

We have plans in place to protect confidentiality of all participants and all identifying characteristics will be de-identified.