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)

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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:** ○ Yale University		

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	○ Mayo Clinic ○ University of North Carolina at Chapel Hill ○ Cooper University Hospital • **NIH Institute:** National Institute on Drug Abuse (NIDA) • **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). ○ **Primary outcome:** The rate of BUP treatment initiated in the ED (Emergency Department) ○ **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.		

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	○ The only ongoing data capture about continued substance use will be that which is documented in the EHR. ○ 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.		Protocol approved by WIRB on 12/6/2018. Reliance agreements received from all systems in July 2019.
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. • 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	Completed: Per the 7/12/18 discussion, the Collaboratory coordinating center provided the study team with information about the use of other opt-out procedures in pragmatic clinical trials.	Approved as minimal risk.

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	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.		
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	• Completed: The study team revised their supplemental material providing additional information about the protocol and plans for handling	A waiver of informed consent was obtained from WIRB.

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	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] ○ The study is minimal risk ○ The study is impracticable without waiver of consent ○ The study does not adversely affect patients' rights/welfare ○ Where appropriate, study subjects will be provided with additional information about their participation • Consistent with a minimal risk study, 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.	data/protecting patient privacy. • Completed: Per the 8/6/18 discussion, the coordinating center has provided the study team with the OHRP guidance on coded private information use in research.	

[1] 45 CFR 46.116

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	• 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.		
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		Study team plans to have an independent study monitor for data monitoring and oversight. This plan was determined in collaboration with NIDA since this is a minimal risk implementation study of established best practices.

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	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 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.	We clarified additional questions for WIRB prior to approval of the protocol. Drs. Sugarman and Carrithers provided some additional input to prepare for the call. The questions were to explain the rationale for decisions that were made with the Ethics and Regulatory Core.
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): ○ 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. ○ How are data protections articulated in the study protocol, and what are the		• Protocol manuscript published in BMJ Open May 30, 2019 at https://bmjopen.bmj.com/content/9/5/e028488 • Waiver of informed consent was approved by WIRB.

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	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 well as notification of publications to open-access journals and articles attributable to the study, in which results of the study will be disseminated.		

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	○ Will consent issues/determinations apply to both patients and physicians? They will apply only to physicians as the human subjects of this trial. ○ 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. ○ 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. ○ 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		

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	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. ○ 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.		