



NIH Collaboratory Ethics and Regulatory Core: UG3 Consultation Call
Behavioral Economic and Staffing Strategies to Increase Adoption of the ABCDEF Bundle in the ICU (BEST-ICU)
August 9, 2023; 11:00 am-12:00 noon ET (via Zoom)

Attendees:

- Core, Coordinating Center, and NIH: Alex Fist (Duke University), Beda Jean-Francois (NCCIH), Karen Kehl (NINR), David Magnus (Stanford University), Stephanie Morain (Johns Hopkins University), Pearl O’Rourke (retired), Tammy Reece (Duke University), Damon Seils (Duke University), Mihaela Stefan (NHLBI)
- Demonstration Project team: Breanna Hetland (University of Nebraska Medical Center), Eduard Vasilevskis (Vanderbilt University Medical Center)

AGENDA ITEMS	DISCUSSION	ACTION ITEMS	CURRENT STATUS as of October 17, 2024
Brief review of Demonstration Project	<p>Meeting attendees received the Specific Aims, Research Strategy, and Resource Sharing Plan for BEST-ICU with the meeting agenda (see supplementary materials attached). Pearl O’Rourke facilitated the discussion. Core members, study team members, NIH representatives, and staff from the NIH Pragmatic Trials Collaboratory Coordinating Center introduced themselves. The BEST-ICU team members present included co–principal investigator Ed Vasilevskis and coinvestigator Breanna Hetland.</p> <p>Project overview: Ed Vasilevskis gave an overview of the project. This is an implementation study of an accepted ABCDEF bundle of interventions aimed at ICU patients to reduce delirium in intensive care unit (ICU) settings. Prevalence of bundle uptake and completeness of implementation are known to affect outcomes. They are proposing a hybrid type III effectiveness-implementation trial to increase uptake of the ABCDEF bundle by comparing 2 implementation strategies: (1) real-time audit and feedback on team-based performance; and (2) a registered nurse implementation facilitator. The 3 partnering healthcare systems use EPIC-based electronic health records,</p>		There have been 2 key changes: (1) ICUs will have the option to either continue the intervention or stop the intervention during the final period; and (2) as a result of consultations with the Ethics and Regulatory Core and the Biostatistics and Study Design Core, the study is using constrained covariate randomization to achieve a higher likelihood of balance of baseline factors that

Approved: October 2, 2023

These minutes were circulated to all participants in the call for 1 round of review and reflect all corrections that were received. The project’s Specific Aims, Research Strategy, and Resource Sharing Plan are included as supplementary material.

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	<p>which should facilitate implementation if one or both interventions is effective.</p> <p>Healthcare system partners: Nebraska Medical Center, Ohio State University Wexner Medical Center, University of Iowa Hospitals and Clinics</p> <p>NIH Institute Providing Oversight: National Heart, Lung, and Blood Institute (NHLBI)</p> <p>Study design: The study will be a stepped-wedge cluster randomized trial, with randomization at the unit level.</p> <p>Outcomes: The primary outcomes are the proportion of units that implement the ABCDEF bundle and the completeness of implementation. Secondary outcomes will include duration of mechanical ventilation; ICU, hospital, and 30-day mortality; ICU and hospital length of stay; days with acute brain dysfunction; discharge disposition, psychoactive medication, and physical therapy utilization; and 30-day hospital readmission.</p> <p>Pearl O’Rourke asked why the study team is proposing a stepped-wedge design rather than parallel randomization. Ed Vasilevskis responded that the decision was based in large part on the feasibility of simultaneous rollout across units. While aware of the risks of this approach, the study team feels confident there will not be interruptions that would increase or decrease implementation of the interventions.</p> <p>Pearl O’Rourke also asked about the rationale for randomization at the ICU level. Ed Vasilevskis responded that, while there is a global ICU culture, there definitely is also a unit-level culture, which makes randomization at this level appropriate. David Magnus recommended that the study team review the December 9, 2022, Rethinking Clinical Trials Grand Rounds presentation by Monica Taljaard, as well as the following paper:</p>		<p>may be associated with bundle performance.</p>

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	<ul style="list-style-type: none"> <li data-bbox="474 175 1339 310">Federico CA, Heagerty PJ, Lantos J, et al. Ethical and epistemic issues in the design and conduct of pragmatic stepped-wedge cluster randomized clinical trials. <i>Contemp Clin Trials</i>. 2022 Apr;115:106703. doi: 10.1016/j.cct.2022.106703. Epub 2022 Feb 15. PMID: 35176501. <p data-bbox="428 354 1346 488">Stephanie Morain asked about inclusion of a washout period. Ed Vasilevskis responded that, as an implementation scientist, he is interested in including a washout period if the interventions are not effective. David Magnus expressed support for this considering this.</p> <p data-bbox="428 532 1346 1130">Pearl O'Rourke asked about intervention fidelity, given the potential rotation of clinical staff among ICUs. Ed Vasilevskis responded that the audit-and-feedback intervention will use a unit-level display of unit-level performance. It is possible that staff movement between units would affect unit-level outcomes. It will be important for the study team to understand how often staff are moving between units. For the nurse facilitator intervention, it is possible there will be an effect on outcomes from staff moving between units. David Magnus observed that this will likely mean a small bias to the null. He asked, given the small number of clusters, whether the study team is worried about the need for a robust effect size. Ed Vasilevskis responded that the team's belief about effect size is that they are starting from a position of low performance. Breanna Hetland added that there will be standardized education across units related to the audit-and-feedback intervention. Thus, at baseline, regardless of staff movement between units, everyone will receive that standard training. The study team also has good connections at each site that will allow them to know what is happening in the units and connect that information to the study data.</p> <p data-bbox="428 1174 1339 1343">Pearl O'Rourke asked about inclusion and exclusion criteria for different categories of patients, such as postoperative patients who only need ventilation overnight, as compared with patients with sepsis who may need ventilation for 2 weeks. Ed Vasilevskis agreed that these populations are different and added that the study team is currently working on the inclusion</p>		

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	<p>and exclusion criteria. Patients in the study population of interest require ventilation for at least 24 hours. So the study team anticipates the audit-and-feedback dashboard will start at day 2. Another population that would likely be excluded are patients receiving chronic ventilation. David Magnus asked whether patients undergoing extracorporeal membrane oxygenation (ECMO) would be excluded. Ed Vasilevskis replied yes.</p>		
<p>Status of IRB approval</p>	<p>The study will use the University of Nebraska Medical Center (UNMC) IRB as the single IRB of record.</p> <p>The study team has obtained IRB approval for focus group activities in the UG3 phase. They are currently working on the trial protocol for the UH3 phase for submission to the IRB and the DSMB.</p>		<p>All sites have received IRB approval.</p>
<p>Risk (Does the project meet regulatory criteria for being considered minimal risk?); and consent (planned processes for relevant subjects)</p>	<p>The study team anticipates that the project will meet the regulatory criteria to be considered minimal risk.</p> <p>The study team plans to seek a waiver of consent. The study will obtain agreement at the ICU level rather than from individual clinicians. The study team has not yet considered whether and how to provide notification to clinicians and patients. Breanna Hetland added that the ABCDEF bundle is currently ordered on all patients at UNMC, so patients aren't able to decline the bundle elements. For the audit-and-feedback intervention, this strategy simply places the information in front of clinicians in a new format to show unit-level performance. Ed Vasilevskis clarified that the ABCDEF bundle itself is not the intervention, as it is already the standard of care in all 3 partnering healthcare systems. David Magnus suggested that this may not be considered human subjects research, but rather could be a considered quality-assurance activity to audit and evaluate whether units are following the standard of care. He added that it may not even require a waiver of consent.</p>		<p>The study team received a waiver of consent. The study team is notifying patients and providers of the study through unit-based notifications and unit-level communications.</p>

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	<p>Pearl O’Rourke asked whether the study team will seek a waiver of consent for Aim 2, which will examine patient-level outcomes. Ed Vasilevskis replied yes.</p>		
<p>Privacy (including HIPAA)</p>	<p>Outcomes will be measured at the unit level, rather than at the provider level. A limited dataset for patient-level outcomes will be deidentified and shared via a PCORI DataMart. The study team is in the process of completing the data use agreements.</p>		<p>Data use agreements are now in place.</p>
<p>Monitoring and oversight</p>	<p>The study team intends to use a data and safety monitoring board (DSMB) and has begun identifying its members. They include implementation scientists, a biostatistician, a critical care physician, critical care bioethicists, a nurse, and bio- and clinical informaticians.</p>		<p>The DSMB makeup is the same as described. The DSMB and the Cores were influential in the changes described above.</p>
<p>Issues beyond this project (regulatory and ethics concerns raised by the project, if any)</p>	<p>Pearl O’Rourke suggested that the study team review the FDA’s June 2023 Content of Premarket Submissions for Device Software Functions: Guidance for Industry and Food and Drug Administration Staff. Ed clarified that the intervention involves only sharing of information rather than clinical decision support. Stephanie Morain expressed appreciation that the study team is framing the intervention as one that simply provides information about what clinicians should already be doing.</p> <p>David Magnus noted that there are questions about when a cluster randomized trial is the appropriate design and that he agrees cluster randomization is appropriate for this study.</p> <p>Mihaela Stefan asked whether there is an obligation to inform patients and clinicians that they are part of the study. David Magnus responded that, even with a waiver of consent, there can be notification strategies. He asked whether the study team has a notification strategy that is specific to the trial</p>	<p>Distribute O’Rourke manuscript to the group [Tammy Reece]</p> <p>[Completed]</p>	<p>As noted above, the study team received a waiver of consent. The study team is notifying patients and providers of the study through unit-based notifications and unit-level communications.</p>

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	<p>or one that is about research occurring at the site more generally. Ed Vasilevskis responded that he would appreciate any resources the group can share on this topic. He would not be opposed to notifying all ICU providers that the study is occurring, but he is unsure how to accomplish this at the patient level. Pearl O'Rourke agreed that the study team should consider notification of ICU providers. Breanna Hetland responded (in the chat box): "In my previous research at Nebraska Med, we've put a poster with a QR code that scans to a 2 minute video about the trial. Damon Shared a link to the "Mechanisms for Notification" section of the Consent, Waiver of Consent, and Notification chapter of the Living Textbook of Pragmatic Clinical Trials. Pearl O'Rourke noted that she would send a draft manuscript on this topic to Tammy Reece for distribution to the group.</p>		
Other matters	None.		
Additional follow-up information			The study team has encountered no other ethical or regulatory issues to this point.