



**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	OWNER
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><b>Project overview:</b> 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, which should facilitate implementation if one or both interventions is effective.</p>		

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><b>Healthcare system partners:</b> Nebraska Medical Center, Ohio State University Wexner Medical Center, University of Iowa Hospitals and Clinics</p> <p><b>NIH Institute Providing Oversight:</b> National Heart, Lung, and Blood Institute (NHLBI)</p> <p><b>Study design:</b> The study will be a stepped-wedge cluster randomized trial, with randomization at the unit level.</p> <p><b>Outcomes:</b> 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 <a href="#">December 9, 2022, Rethinking Clinical Trials Grand Rounds</a> presentation by Monica Taljaard, as well as the following paper:</p> <ul style="list-style-type: none"> <li>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. <a href="#">PMID: 35176501</a>.</li> </ul> <p>Stephanie Morain asked about inclusion of a washout period. Ed Vasilevskis responded that, as an implementation scientist, he is interested in including a</p>		

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	<p>washout period if the interventions are not effective. David Magnus expressed support for this considering this.</p> <p>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>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 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>		
Status of IRB approval	The study will use the University of Nebraska Medical Center (UNMC) IRB as the single IRB of record.		

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	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.		
Risk (Does the project meet regulatory criteria for being considered minimal risk?); and consent (planned processes for relevant subjects)	<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>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>		
Privacy (including HIPAA)	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.		
Monitoring and oversight	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.		

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Issues beyond this project (regulatory and ethics concerns raised by the project, if any)	<p>Pearl O'Rourke suggested that the study team review the FDA's June 2023 <a href="#">Content of Premarket Submissions for Device Software Functions: Guidance for Industry and Food and Drug Administration Staff</a>. 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 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 <a href="#">"Mechanisms for Notification" section</a> 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>	Distribute O'Rourke manuscript to the group [Completed]	<b>Tammy Reece</b>
Other matters	None.		

## SPECIFIC AIMS

Millions of survivors of critical illness worldwide experience profound and frequently persistent physical, mental, and cognitive health impairments that are often preventable through the application of existing knowledge. These impairments are commonly acquired in the intensive care unit (ICU) and are often initiated and/or exacerbated by known racial and socioeconomic health disparities and outdated mechanical ventilation (MV) liberation and symptom management practices. Indeed, ICU-acquired pain, anxiety, delirium, and weakness are associated with numerous adverse health outcomes including prolonged MV, mortality, functional decline, new institutionalization, and severe neurocognitive dysfunction. A robust body of research demonstrates that clinical outcomes improve when integrated, interprofessional approaches to MV liberation and symptom management are applied early in the course of critical illness. One such approach is the ABCDEF bundle. When applied in everyday practice, ABCDEF bundle performance is consistently associated with meaningful improvements in important patient and healthcare system outcomes. Unfortunately, ABCDEF bundle performance remains unacceptably low as clinicians struggle with multiple barriers to bundle delivery. Our previous work demonstrates bundle-related clinical decision making is indeed complex and frequently influenced by prevailing ICU social norms, common knowledge deficits, and substantial workflow challenges. Missing from the literature are evidence-based implementation strategies that are adaptable, responsive to community needs, and account for the cultural and organizational factors necessary to increase bundle adoption particularly in traditionally under-resourced settings like safety net hospitals. Until this key gap in knowledge is filled, the excessively high morbidity, mortality, costs, and disparities associated with critical care delivery will continue and the public health benefit of the ABCDEF bundle will not be fully realized.

Congruent with RFA-AT-22-001, the goal of this proposal is to support the “real world” assessment of strategies used to foster adoption of several highly efficacious evidence-based practices in healthcare systems that provide care to critically ill adults with known health disparities. Based on strong preliminary data, the study’s overall objective is to evaluate two discrete strategies grounded in behavioral economic and implementation science theory to increase adoption of the ABCDEF bundle in critically ill adults. The strategies being evaluated target a variety of ICU team members and known behavioral determinants of ABCDEF bundle performance. The proposed project includes two phases and four specific aims.

In **Phase 1 (UG3)** we will work with the NIH’s Healthcare System Research Collaboratory Coordinating Center and our community partners to: (1) further develop and validate study-related electronic data methods and quality control metrics; (2) complete selection of clinically relevant and socially meaningful short and long-term outcome measures; and (3) finalize the study’s implementation plan, research protocol, and budget.

**UG3 Aim 1:** Enhance and finalize the implementation strategies and research methods used to facilitate and evaluate the effectiveness of ABCDEF bundle adoption.

In **Phase 2 (UH3)** we will conduct a 3-arm, pragmatic, stepped-wedge, cluster-randomized, trial to evaluate both implementation (primary) and clinical (secondary) effectiveness outcomes. After creating 6 matched pairs of 12 ICUs from 3 discrete safety net hospitals (estimated total N=8,100 patients on MV), we will randomly assign ICUs within each matched pair to receive either real-time audit and feedback or a Registered Nurse (RN) implementation facilitator and each pair to one of six wedges. At the end of the 27-month trial, we will continue to collect implementation and clinical outcomes for an additional 3 months to evaluate the effects of removing the implementation strategies. During this time, we will also use mixed methods to assess key stakeholders’ (interprofessional ICU team members, hospital administrators, electronic health record specialists) acceptability of both implementation strategies and how each strategy affects ICU clinicians’ work intensity.

**UH3 Aim 1:** Compare the effectiveness of real-time audit and feedback and RN implementation facilitator on ABCDEF bundle adoption (**primary study outcome**).

**UH3 Aim 2:** Compare the effectiveness of real-time audit and feedback and RN implementation facilitator on clinical outcomes (duration of MV; 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).

**UH3 Aim 3:** Identify and describe key stakeholders’ experiences with, and perspectives on, the acceptability and impact on work intensity of real-time audit and feedback and RN implementation facilitator.

Building on years of successful collaboration, our experienced interprofessional team is ideally suited to perform the proposed work. We expect study results will impact the field by developing equitable, efficient, effective, and replicable ways of accelerating the reliable uptake of the highly efficacious evidence-based ICU interventions contained in the ABCDEF bundle. This will dually address known healthcare disparities and ultimately improve the care and outcomes of millions of critically ill adults annually.

## SIGNIFICANCE

**Millions of survivors of critical illness worldwide experience profound and often persistent physical, mental, and cognitive health impairments.** Each year, over five million Americans are admitted to intensive care units (ICUs) and over one-quarter of all ICU beds in the U.S. are occupied daily by patients receiving mechanical ventilation (MV).<sup>1-4</sup> In-hospital mortality rates for the nearly 800,000 patients who require MV annually are high ( $\geq 35\%$ ) and an estimated \$27 billion is spent each year on this population's acute hospital stay alone.<sup>2,4</sup> These numbers will rise as the number of adults with complex comorbidities grows, our population ages, and the incidence of acute respiratory failure increases.<sup>5,6</sup> While ICU survival rates have improved, this survival often comes with heavy personal and financial costs.<sup>7</sup> Many ICU survivors experience new and often profound physical, cognitive, and mental health impairments that may persist for years after hospital discharge.<sup>8,9</sup> The constellation of these impairments is termed Post Intensive Care Syndrome (PICS). Strong and growing evidence indicates the incidence and severity of PICS is related to pre-existing risk factors, racial and socioeconomic health disparities, and commonly acquired ICU conditions that are initiated and/or exacerbated by outdated MV liberation and symptom management practices.<sup>10-14</sup>

**Commonly acquired ICU conditions affect both the quantity and quality of life after critical illness.** ICU patients commonly experience symptoms that cause acute suffering and have long-lasting effects.<sup>13,14</sup> Pain, experienced by  $\geq 70\%$  of patients, is distressing, often under-treated, and often present with routine ICU activities (tracheal suctioning, turning) and at rest.<sup>15-17</sup> Delirium, occurring in up to 80% of patients requiring MV,<sup>18,19</sup> is a particularly poor prognostic indicator. A meta-analysis found delirious patients were 6 times more likely to experience nosocomial complications, 2.5 times more likely to be discharged to skilled placement, and spent 7 days longer on MV than non-delirious patients.<sup>20</sup> Lastly, ICU-acquired weakness, often caused by ICU medications and bedrest, occurs in up to 50% of critically ill patients.<sup>21-23</sup> The effects of ICU pain, delirium, and weakness extend well beyond hospitalization, being consistently associated with increased mortality, functional decline, depression, post-traumatic stress disorder, chronic pain, and severe long-term neurocognitive impairment.<sup>13,14,23-36</sup>

**Highly efficacious and safe MV liberation, symptom management, and mobility interventions exist.** In 2018, the Society of Critical Care Medicine (SCCM) released their Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) in Adult ICU Patients.<sup>14</sup> Current and past PADIS Guidelines recommend several evidence-based interventions to improve patient outcomes.<sup>13,14</sup> These interventions include: (1) routine monitoring of pain, level of arousal, and delirium using valid and reliable tools; (2) maintaining patients at a "light" level of sedation by using daily spontaneous awakening trials (SATs), target-based sedation protocols, or an analgesia-based sedation approach; (4) avoiding benzodiazepines; and (5) performing early and frequent mobilization. Additional benefit is accrued when SATs are combined with MV discontinuation protocols that include daily spontaneous breathing trials (SBTs).<sup>37-41</sup> Paired SATs/SBTs reduce the number of days patients are on MV (3-day reduction), hospital length of stay (4-day difference), and mortality (for every 7 patients treated with coordinated SATs/SBTs 1 life is saved) when compared with SBTs alone.<sup>39</sup>

**The ABCDEF bundle facilitates adoption of multiple PADIS practices and improves outcomes.** The ABCDEF bundle (**Figure 1**) is an evidence-based, multicomponent, interprofessional approach to optimizing care of the critically ill.<sup>11,12,42</sup> The overarching goal of the bundle is to maximize wakefulness and encourage cognitive and physical activity. These changes occur through daily use of: (1) the PADIS assessment tools; (2) both SATs/SBTs; (3) select sedative/pain medications; (4) standardized mobility activities; and (5) family engagement. The bundle applies to every ICU patient, every day, regardless of MV status or diagnosis (a patient simply receives every bundle element for which she/he is eligible).

In 2014, members of our study team (Balas, Vasilevskis) conducted the first evaluation of the safety and effectiveness of the foundational ABCDEF bundle.<sup>43</sup> This single-center study included data on 296 critically ill adults before (n=146) and after (n=150) bundle implementation. Critically ill patients managed with the bundle experienced significant improvements in ventilator-free days and hospital mortality rates compared to those in the pre-bundle period. After adjustment, patients managed with the bundle experienced nearly half the odds of delirium and increased odds of mobilizing out of bed. A subsequent study of over 6,000 patients supported these positive findings while also demonstrating a "dose-response" relationship to bundle implementation.<sup>44</sup>

Most recently, study MPs (Balas, Vasilevskis) helped conduct and evaluate the SCCM's ICU Liberation Quality Improvement (QI) Collaborative. The goal of this project was to foster widescale adoption

**Figure 1. ABCDEF Bundle**

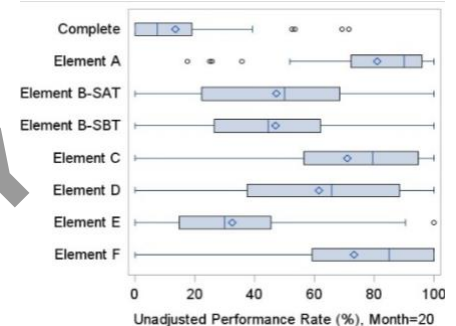




of the society's PADIS guidelines (via the ABCDEF bundle) through a QI collaborative approach.<sup>45,46</sup> The collaborative included over 15,000 critically ill adults across 68 U.S. ICUs from academic, community, and federal hospitals. We found complete bundle performance was associated with significantly lower likelihood of death within 7 days (adjusted hazard ratio, 0.32; CI, 0.17–0.62), next-day MV use (AOR, 0.28; CI, 0.22–0.36), coma (AOR, 0.35; CI, 0.22–0.56), delirium (AOR, 0.60; CI, 0.49–0.72), physical restraint use (AOR, 0.37; CI, 0.30–0.46), ICU readmission (AOR, 0.54; CI, 0.37–0.79), and discharge to a facility other than home (AOR, 0.64; CI, 0.51–0.80).<sup>46</sup> A consistent dose-response relationship between higher proportional bundle performance and improvements in each of these outcomes was also observed (all  $p < 0.002$ ). Combined with other large-scale bundle-related work,<sup>47–54</sup> evidence strongly supports the ABCDEF bundle as a safe and effective intervention for preventing several common ICU-acquired conditions.

**Multiple studies show that many of the evidence-based interventions contained in the ABCDEF bundle are infrequently used in everyday ICU practice.**<sup>55–67</sup> While ICU Liberation collaborative participation led to significant improvements in complete (all eligible bundle elements performed) and proportional (percentage of eligible bundle elements performed) bundle performance, we found there continues to be substantial need for improvement.<sup>67</sup> By the end of the collaborative, complete and proportional bundle performance rates were only 12% and 59% respectively.<sup>67</sup> Furthermore, bundle element performance remained highly variable at the end of the collaborative (**Figure 2**). For example, an average  $\leq 40\%$  of patients participated in early mobility and less than half of patients requiring MV received a daily SBT. We observed similar wide unit-level variability in ICU practices in another analysis of the collaborative,<sup>68</sup> supporting the need to continue to focus on new and innovative strategies to increase bundle adoption in everyday care.

**Figure 2. Variation in Bundle**



**Inconsistent use of evidence-based ICU interventions may be particularly harmful to groups who suffer from known health disparities.** Racial and ethnic differences in healthcare delivery and outcomes are well documented and extend to the ICU.<sup>10,69</sup> People of color and uninsured patients are less likely to be admitted to an ICU and receive fewer ICU interventions (tracheostomy, central venous access) even after adjusting for severity of illness.<sup>70–76</sup> While partially explained by other factors, Black individuals continue to have a higher mortality rate from sepsis and acute lung injury and Hispanic patients suffering from acute respiratory distress syndrome are more likely to die than whites.<sup>10,69</sup> Data also indicates certain racial and ethnic groups are also at higher risk of PICS,<sup>10</sup> and experience worse quality of life and employment outcomes after a critical illness compared to whites.<sup>77,78</sup>

Minority groups are also more likely to receive critical care in hospitals with higher complication, mortality, and readmission rates.<sup>79–84</sup> In a study including 200 U.S. hospitals, almost a third of Black patients and half of Hispanic patients received critical care in just 7% of surveyed hospitals.<sup>84</sup> These minority-serving hospitals showed significantly less decline in critical illness mortality over the last decade, compared to non-minority hospitals.<sup>84</sup> Other studies have documented worse outcomes (failure to rescue, mortality, readmissions) when comparing safety net and non-safety net hospitals, even after controlling for age, race, severity of illness, and socioeconomic status.<sup>79–85</sup> This suggests intrinsic qualities of safety net hospitals (staffing levels, QI experience, electronic health record [EHR] system efficiency) may lead to lower quality and more expensive care. Given these findings, it has been suggested that to address health disparities in the ICU, interventions should focus on increasing the delivery of evidence-based interventions aimed at managing acute organ dysfunction and increasing overall QI efforts at hospitals that care for underserved populations.<sup>10,69</sup>

**ICU clinicians experience substantial challenges when trying to deliver the ABCDEF bundle in everyday care.**<sup>55,86–101</sup> One review found >100 factors believed to influence bundle implementation.<sup>96</sup> These patient, provider, and organizational-level barriers most frequently include workload and staffing levels, knowledge deficits, ineffective communication, care coordination issues, and EHR challenges. Our prior work has also found individual attitudes, social norms, and common cognitive biases influence bundle performance.<sup>46,86,87,88</sup> These biases include clinicians' preference for the current state of ICU affairs (status quo bias), consistent over-estimation of bundle performance (overconfidence bias), and the disposition to judge events, such as self-extubation or falls, as being more likely than they are (availability biases). These findings, and our most recent work (see **Preliminary Studies**), lead us to believe that addressing workload and care coordination burdens while also applying strategies from behavioral economics may improve the likelihood of successful ABCDEF bundle adoption.

**Behavioral economic theory informed interventions aimed at changing clinician behavior are promising and increasingly delivered via EHR systems.** The complexity of decision making, constraints



on time, and fluctuating human and other resources inherent in the ICU environment often cause clinicians to employ mental shortcuts, often called heuristics.<sup>102-108</sup> Our prior work demonstrates that when combined with prevailing social norms and common cognitive biases, these heuristics often lead to errors and poor ABCDEF bundle performance.<sup>46</sup> Thus, interventions rooted in behavioral economics may play an essential role in changing the status quo of everyday ICU practice. Researchers are increasingly using behavioral economic interventions delivered via EHR systems to harness the predictable ways in which human judgement is biased to improve decisions.<sup>109</sup> These interventions, often known as “nudges”, reshape the way options are presented to decision-makers to optimize their choices.<sup>102</sup> One systematic review found the most studied, effective, and least restrictive nudge in healthcare was framing information for clinicians through peer comparison and/or audit and feedback.<sup>110</sup>

While few studies have examined the effect behavioral economic interventions have on ICU decision-making, two recent studies suggest this as a promising area. Bourdeaux et al.<sup>111</sup> evaluated the effects of two nudge-based interventions (default low tidal volume [TV] MV settings and deploying a dashboard that displayed visual cues when TVs were high). They found TVs significantly decreased in the default group, and, in the dashboard intervention, TVs fell more quickly and by a greater amount after a set “red warning” TV was breached when compared with controls. Another, single ICU before-after study<sup>112</sup> found that a web-based real-time audit and feedback dashboard displaying nudges to wean sedation and MV and text message alerts was associated with reductions in MV duration and ICU LOS.

**The proposed “Behavioral Economic and Staffing Strategies To Increase Adoption of the ABCDEF Bundle in the ICU (BEST ICU)” study addresses important gaps in existing knowledge.** Despite its proven safety and effectiveness, adoption of the ABCDEF bundle into everyday practice remains low. There are several reasons for this ongoing knowledge-to-practice gap. First, a pressing implementation challenge includes the amount of work and interprofessional care coordination needed to effectively implement the bundle. Despite dozens of studies documenting the association between nurse staffing and patient outcomes in the acute care setting,<sup>113</sup> no RCTs to date have evaluated the effectiveness of adding a Registered Nurse (RN) implementation facilitator to the ICU team whose specific responsibility is to assist with and coordinate daily delivery of the evidence-based interventions in the ABCDEF bundle. Second, most ICU studies to date have taken a “kitchen sink” approach to ABCDEF bundle implementation, where a variety of strategies are suggested for use, but the utility of any single implementation strategy is never evaluated. This gap leads to uncertainty as to what is the most effective way of increasing bundle adoption. Third, we know little about how time affects bundle implementation efforts. It is possible an implementation strategy that is effective in the short-term wanes over time, or a strategy that is initially ineffective takes longer to work. Finally, the ongoing COVID-19 pandemic has heightened demands on ICU clinicians. Our study will evaluate whether the tested strategies are acceptable to a currently stressed ICU workforce and the effect the interventions have on clinicians’ work intensity.

## INNOVATION

The work proposed in this application is innovative because it represents the first translational research trial specifically aimed at developing and testing theory-based, clinician-informed, pragmatic, and potentially sustainable ABCDEF bundle implementation strategies. The following are key conceptual and methodologic innovations of the proposed work:

- **Reduces healthcare disparities through increased adoption of evidence-based ICU interventions.** The proposed study will occur in three discrete medical centers that serve as safety net hospitals for their local, regional, and state communities. They also serve as referral centers for patients living in rural areas, a population that experiences significant health disparities and is underrepresented in NIH research. A goal of the ABCDEF bundle is to provide consistent, guideline-based, standardized care in a safe and equitable manner. This type of care reduces opportunities for implicit bias and potentially detrimental social norms to influence everyday clinical decision-making. We will examine implementation and clinical effectiveness outcomes by important social disparity metrics (race, ethnicity, insurance status, ZIP code). This provides the opportunity to assess if increased bundle adoption improves outcomes across a range of vulnerable groups.
- **Draws from established behavioral change theories that are currently underutilized in the ICU.** A range of highly effective behavioral economic and implementation science theory-informed interventions have been developed and tested in a variety of healthcare settings. Unfortunately, few of these interventions have been tested in the high-risk and expensive ICU setting where their application could be potentially beneficial.<sup>114</sup>
- **Alters the current ICU team paradigm and addresses key stakeholders’ concerns.** ICU team members consistently cite workload and care coordination as major barriers to effective ABCDEF bundle adoption. This proposal directly addresses these concerns by rigorously testing the effects of a RN implementation facilitator to aid the complex care coordination, communication, and work required to effectively implement the bundle. This novel role, if proven effective, could shift the current paradigm of the existing ICU team structure to include a “quarterback” that leads ABCDEF bundle delivery. Moreover, while the implementation strategies selected for study are explicitly based on key stakeholder feedback, the effect these strategies have on ICU clinicians’

workload and whether clinicians find the strategies acceptable has yet to be determined. This knowledge is critical considering the unprecedented demand for ICU services imposed by the COVID-19 pandemic and the unsustainable physical, cognitive, and psychological stress currently placed on ICU clinicians.

- **First-of-kind, multi-site study to test specific ABCDEF bundle implementation strategies and explore longer-term patient outcomes.** Although strong evidence supports the benefits of the ABCDEF bundle, there is currently limited data to support using one implementation strategy over another to increase bundle adoption or improve clinical outcomes, and no fully powered multi-site RCTs exploring this important issue. Considering the low worldwide adoption of the bundle, it is imperative we study specific implementation methods to increase the likelihood of adoption across diverse healthcare systems and in populations with known health disparities. To our knowledge, this will also be the first fully powered RCT exploring the effect the ABCDEF bundle has on longer-term patient outcomes (post-discharge mortality, 30-day hospital readmission). Therefore, our results will provide policy makers, payers, and healthcare providers with new data that can be used to assess potential models for improving existing healthcare delivery.
- **Uses a novel study design while building upon currently available EHR technology and established patient-centered outcomes research network capability.** This will be one of a few multicenter, Hybrid Type 3 effectiveness-implementation trials conducted in the ICU setting using a randomized, stepped wedge design. It will also be the first to use the new EHR software from EPIC® that incorporates ABCDEF bundle interventions into clinicians' workflows and established resources from the National Patient-Centered Clinical Research Network (PCORnet) where health data, research expertise, and patient insights are available to deliver fast, trustworthy answers that advance health outcomes (see **Preliminary Studies**).

## APPROACH

### Study Overview

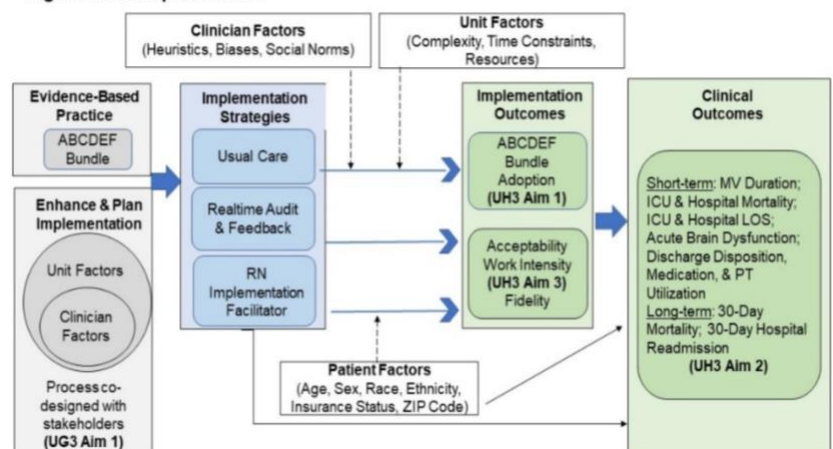
Congruent with RFA-AT-22-001, the overall goal of this proposal is to support the “real world” assessment of strategies to foster adoption of several evidence-based clinical practices in healthcare systems that provide care to critically ill adults and in populations with known health disparities. Our project specifically focuses on building and evaluating behavioral economic and implementation science theory-based interventions fostering ABCDEF bundle adoption and improving the clinical outcomes of critically ill adults. The proposed project includes two phases that are completed over 5 years. In **Phase 1 (UG3)**, we will work with the NIH's Healthcare System Research Collaboratory Coordinating Center and our community partners to further develop and tailor the implementation strategies and measures used to assess implementation and clinical effectiveness in the proposed clinical trial. In **Phase 2 (UH3)**, we will conduct a pragmatic, stepped-wedge, cluster-randomized hybrid type III effectiveness-implementation trial. The two strategies to be studied include real-time audit and feedback and RN implementation facilitation. These strategies were selected based on our extensive preliminary work that has identified the key barriers to ABCDEF bundle delivery, various personal and social determinants of bundle-related behaviors, and ICU clinicians' perspectives on which implementation strategies are most likely to lead to bundle adoption and long-term adherence. Complementing the trial, we will use mixed methods to assess key stakeholders' acceptability of the implementation strategies and how each strategy affects ICU clinicians' workload.

### Research Framework

The Consolidated Framework for Implementation Research (CFIR)<sup>115</sup> and behavioral economic theory frame all aspects of the proposed work (**Figure 3**). Our team has used the CFIR in multiple studies and settings, most recently to guide the development, implementation, and evaluation of the ICU Liberation Collaborative.<sup>89</sup> The CFIR provides a taxonomy of operationally defined constructs that influence implementation of complex programs like the ABCDEF bundle. The CFIR organizes 39 constructs across 5 major domains. This study will focus primarily on the CFIR's inner setting, characteristics of individuals, and implementation process domains.

The implementation strategies being tested were derived from behavioral economic theory. Using insights from psychology and other social sciences, the central premise of behavioral economics is that when confronted with limited resources (ability, time, information), people do not make the same decisions as if complete and

Figure 3. Conceptual Model



certain information were available.<sup>102-108</sup> Behavioral economists have shown that decision-making is sensitive to context and subject to influence by seemingly trivial details in the social and physical environment that influence and constrain human behavior. When making high-volume decisions under conditions of uncertainty, decision making can be guided by mental shortcuts.<sup>102-106</sup> While these shortcuts can be adaptive in complex environments like the ICU, they are also vulnerable to known cognitive biases that can ultimately lead to reduced quality and disparities in healthcare.

### Experience of the Research Team

Collectively, the skills, complementary expertise, and interprofessional nature of our study team make us ideally prepared to design and test implementation strategies that reflect the preferences, resources, and culture of the participating sites and future end users. Dr. Balas (MPI) is a nurse-scientist with expertise in ICU symptom management, the ABCDEF bundle, participatory action research, and QI. She has conducted mixed-methods research for over 15 years with extensive experience in the design, conduct, and evaluation of large-scale dissemination and implementation studies. Dr. Vasilevskis (MPI) is a physician-scientist and hospitalist with an extensive history of health services research including the recent successful completion of a pragmatic RCT that followed patients in over 20 post-acute care sites (NIA - R01AG053264). Drs. Balas and Vasilevskis have worked together for over a decade serving as investigators on many of the preliminary studies leading to this proposal.

The team includes highly experienced Co-Is (see **Clinical Trial Experience** table) with the specific and unique qualifications necessary to effectively complete the proposed work. Dr. Campbell, an internationally recognized leader in the field of bioinformatics and EHR standardization, will serve as overall PCORNet datamart manager and oversee the multisite EHR data collection, storage, and management processes. Dr. Hetland (critical care nurse-scientist), Mr. Ultican (Director of Data Warehousing and Analytics at the NMC), Dr. Blum (anesthesiologist/intensivist and Chief Medical Officer at the UIHC), and Dr. Exline (physician-scientist and OSU-WMC MICU director) will work together to incorporate and standardize the necessary EHR changes for the real time audit and feedback dashboard and multisite outcomes assessment. The study will be informed by leaders in all areas of ABCDEF bundle implementation (pain, sedation, and delirium management [Balas, Vasilevskis], MV liberation [Exline, Blum], ICU medication management [Dr. Gerlach], early mobility [Dr. Krupp], and family engagement [Hetland]) and include experts in healthcare disparities (Dr. Horner, Dr. Kim), cognitive work analysis (Krupp), organizational research (Kim, Horner), and interventions to improve provider wellbeing (Horner) that will be critical in study implementation and mixed-method analysis. Dr. Wichman will lead statistical analyses, bringing his expertise designing and analyzing large-scale clinical trials, including those using step-wedge designs. Dr. Halpern, a senior investigator at the University of Pennsylvania's Center for Health Incentives & Behavioral Economics, will serve as our behavioral economic consultant. Finally, day-to-day study operations and RN implementation facilitator oversight will be led by Drs. Hetland, Krupp, and Gerlach who have strong established relationships with clinicians and administrators at the study sites (see **Letters of Support**).

### Preliminary Studies

In addition to our work describing the safety, effectiveness, and low adoption rates of the ABCDEF bundle in everyday ICU practice<sup>44,46,67</sup> we completed several other studies funded by our preparatory grant from the NHLBI (1 R01 HL146781-01) and other sources that further strengthen the scientific premise for the proposed work.

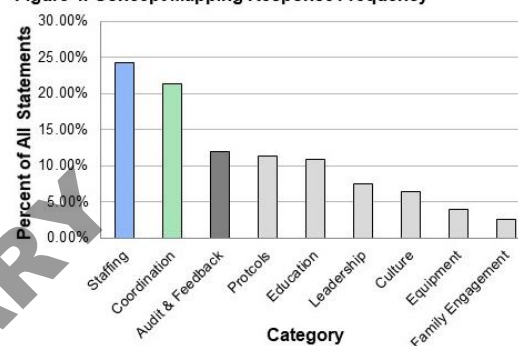
**Disparities exist in ABCDEF bundle performance.** Our prior work utilizing EHR data from 977 critically ill adults admitted to 15 ICUs in 7 community hospitals demonstrates ABCDEF bundle performance varies by race and ethnicity.<sup>116</sup> We found pain assessments (bundle element A) were significantly more likely to be completed in Black and white patients compared to Asians, and Hispanic patients had half the odds of having delirium assessments performed compared to non-Hispanics (bundle element D). After adjusting for severity of illness, days on MV, site, and time, overall bundle performance was found to be significantly lower for Hispanic patients ( $F=23.72$ ,  $p<0.01$ ). These findings add to the ICU disparity literature and support the need for more equitable delivery of evidence-based ICU practices, including the ABCDEF bundle.

**Unit factors predict SBT delivery.** SBTs and SATs are among the least adhered ABCDEF care processes. To better understand variability in bundle performance, we recently completed an analysis of the ICU Liberation Collaborative dataset to determine what factors are associated with SBT performance (similar findings for SAT).<sup>86</sup> This analysis included 4,938 critically ill adults who received MV during their ICU stay. We performed mixed-effects logistic regression modeling, created receiver operating characteristic curves, and calculated area under the curve (AUC). In multivariable models controlling for admitting patient characteristics, factors independently associated with higher odds of a next-day SBT included documented sedation targets, more frequent level of arousal assessments, and dexmedetomidine use. Factors independently associated with lower odds of a next-day SBT included deep levels of sedation and benzodiazepine or ketamine use. Finally, we found that when unit-level fixed effects were added to the models there was a substantial increase in AUC from 0.653 (0.643-0.663) to 0.715 (0.706-0.724). This suggests that unit-specific characteristics (staffing, workload, culture) may play an important role in predicting SAT or SBT performance on any given ICU day.

**Provider and organizational-level factors cause extubation delays in everyday ICU practice.** We (Balas, Exline) recently conducted a study exploring clinicians' perceptions of barriers and facilitators to timely extubation after a successful SBT.<sup>117</sup> An online survey was administered to 135 interprofessional team members across three OSU-WMC ICUs. Most clinicians surveyed (80%) believed the current SBT and extubation process took too long and led to negative patient outcomes. The most cited factors leading to extubation delays included care coordination issues and communication failures. Clinicians reported increased staffing and closer patient surveillance would improve extubation rates. For example, it was offered that MV liberation would be more likely if a busy RN/RT would have extra help and be comfortable allowing another RN/RT to "fill in" (perform, observe, or comfort a patient during a SAT/SBT) if they could not be present. It was also noted that once a SAT/SBT was completed, there was often inadequate staffing to safely extubate a patient. Clinicians deemed extubation as a high-risk, high-reward procedure, that would benefit from the additional RN facilitation found in this proposal.

**Clinicians have insights into strategies that would optimize bundle performance.** We are completing a concept-mapping study to better understand the insights of front-line ICU clinicians regarding the key to successful bundle implementation. As part of the concept mapping exercise, front-line clinicians (RNs, RTs, PTs, physicians) were asked to complete the following focus prompt: "To successfully deliver the ABCDEF bundle on a daily basis in the ICU, a specific thing that should be in place or included is..." Thus far, we received 181 individual responses from over 100 clinicians. Preliminary analysis yields responses categorized into at least 9 intervention types (**Figure 4**). Staffing, coordination, and the use of EHR systems to facilitate audit and feedback were described as strategies "that should be in place" for daily ABCDEF practice. The responses informed the proposed research to understand the effect of RN nurse facilitation and audit/feedback to drive ABCDEF adoption.

Figure 4. Concept Mapping Response Frequency



**The ABCDEF bundle has been recently adopted into common EHR software.** Dr. Balas assisted the SCCM in creating an ICU Liberation (ABCDEF bundle) Implementation Toolkit for critical care providers to measure their practice for QI. The toolkit includes a booklet with operational definitions for each bundle element, example data and compliance metrics, and a spreadsheet for data collection. Until recently, this toolkit required manual data input. Now, two of the largest health information technology companies, Epic® and Cerner®, include the ICU Liberation Bundle in their EHR software. In Epic, an organization can implement the ICU Liberation toolkit using existing flowsheets, procedures, application reports, activity and navigator records, BestPractice Advisories, and tasks. Building off this software, members of our study team (Hetland, Ultican) recently created an interactive, dynamic, real-time dashboard in the Epic EHR that tracks both process and outcome metrics specific to the ABCDEF bundle and is transferable for use in other healthcare systems. Ultimately, this dashboard will be used to provide real-time audit and feedback in the proposed work.

## Methods- Phase 1- UG3

In Phase 1 (**UG3 Phase; 1 year**), we will work with the NIH's Healthcare Systems Research Collaboratory Program's Collaboratory Coordinating Center and our community partners to further develop, tailor, and finalize the strategies and measures that will be used to assess both implementation and clinical effectiveness in the proposed trial.

**Table 1** provides the core UG3 milestones (timeline and further details provided in **PHS Human Subjects and Clinical Trial Information** form). We believe these data, process, and quality preparations will increase the study's rigor and validity and lead to a greater understanding of the effectiveness of each implementation strategy. This will resultantly facilitate translation into ICU practice, improve care, and reduce disparities in vulnerable populations.

**Milestones 1-3** involve study-specific preparatory work. The first milestone will involve installing and testing the newly created

real-time audit and feedback dashboard. Led by Hetland, Ultican, Blum, and Exline, we will first convene an Epic work team at all three participating sites. Next, the NMC site will document, share, and assist with the installation of the real-time audit and feedback dashboard built within the existing Epic ICU Liberation software with the

Table 1. UG3 Phase 1 Milestones

<b>Milestone 1:</b> Install & test newly created real-time audit & feedback dashboard. (Hetland, Ultican, Exline, Blum)
<b>Milestone 2:</b> Develop, test, & deploy PCORnet datamart changes to support study data management & accrual. (Campbell, Exline, Blum)
<b>Milestone 3:</b> Engage ABCDEF process owners in conducting a local needs assessment & developing detailed plans for site implementation. (Balas, Vasilevskis, Krupp, Gerlach)
<b>Milestone 4:</b> Collaborate with the NIH's Healthcare Systems Research Collaboratory Program's Collaboratory Coordinating Center work groups to further develop practices that will be implemented across three healthcare systems. (Balas, Vasilevskis, Campbell, Hetland, Exline, Gerlach, Blum, Krupp, Horner, Kim, Wichman)
<b>Milestone 5:</b> Address all ethical issues & issues related to human subject safety oversight for the project (Balas, Vasilevskis)
<b>Milestone 6:</b> Develop detailed budget for conduct and completion of trial (Balas, Vasilevskis)
<b>Milestone 7:</b> Finalize detailed plans for data coordination and quality control for the UH3 phase (Balas, Vasilevskis, Campbell, Wichman)
<b>Milestone 8:</b> Finalize research protocol & submit to IRB (Balas, Vasilevskis)



UIHC and OSU-WMC Epic teams. Once installed, all sites will validate software function and train site staff in any new ICU documentation necessary to the study intervention.

For the second milestone, we will develop, test, and deploy the PCORnet datamart changes to support study data management and accrual. All three proposed sites are active participants in PCORnet and quarterly extract their Epic EHR data into deidentified datamarts standardized with the PCORnet Common Data Model v6.0 (CDMv6)[ref]. PCORnet Research query protocols will be employed throughout the study to retrieve, aggregate, and deliver historical performance, process, and clinical outcomes data for trial management, safety monitoring, and statistical analyses. In the UG3 phase, the NMC data coordination center (led by Campbell) will: (1) develop and standardize the research data inventory and codify all study facts with standard terminologies; (2) prepare new CLARITY® data extracts for extract of new study data structures needed at UIHC & OSU-WMC and collaborate on their installation and testing; (3) prepare, document, test, and deploy data validation queries for use in data quality checks at all sites; (4) develop and deploy data use agreements for all sites and coordinate central IRB authorization agreement for study data management plans; (5) validate CDMv6 data formatting and compliance at all sites; (6) implement and test Amazon Web Services(AWS) S3 service for research data transfer; (7) develop study research database at UNMC as landing site for study data; (8) design, test, and validate data pull software for data reporting and integration into the landing site repository; and (9) collaborate with the statistician on data design and curation. By UG3 end, all sites will be study-ready to support data management and accrual compliant with PCORnet protocols.

Finally, in milestone 3, Balas, Vasilevskis, Krupp, and Gerlach will engage ABCDEF process owners in conducting a local needs assessment and developing detailed plans for site implementation to help inform implementation strategy refinements and further understand potential barriers/facilitators to site-specific bundle performance. To accomplish this, we will collect each site's current bundle policy and assess if it is consistent with the best available evidence. If needed, we will work with study sites to seek potential changes. Next, we will conduct focus group interviews at each site. Here, we will provide attendees a description of the implementation strategies and encourage them to provide feedback on ways each could be improved or locally adapted, with a specific emphasis on meeting the needs of populations suffering from known health disparities.

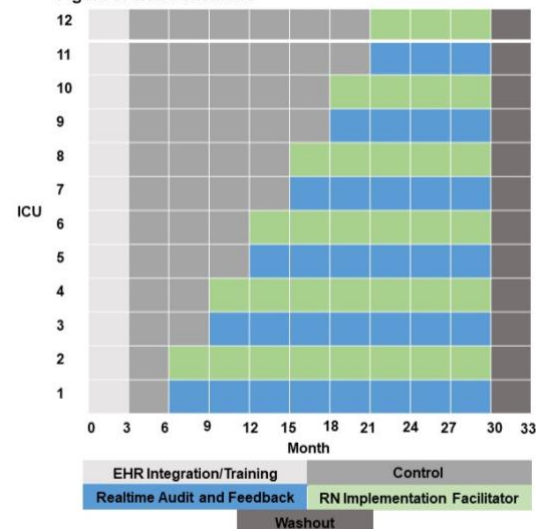
## Methods- Phase 2- UH3

**Study Design and Randomization.** In Phase 2 (**UH3; 4 years**) we will conduct a 3-arm, pragmatic, stepped-wedge, cluster randomized hybrid type III effectiveness-implementation trial across 12 ICUs from 3 safety net hospitals. We will also use mixed methods to assess key stakeholders' experiences with, and perspectives on, the acceptability of the tested implementation strategies and how each affects clinical staff's workload. An overview of the trial design is provided in **Figure 5**.

The unit of randomization will be the ICU. ICUs will be randomly assigned to either real-time audit and feedback (strategy A) or RN implementation facilitation (strategy B) using a two-step, block randomization with hospital as the block. First, 2 ICUs each will be randomly assigned to switch onto a strategy in the first, then second time period within their respective block. The second randomization will assign 1 of the 2 ICUs to either strategy A or B, with the second ICU being assigned the opposite strategy. During the trial, all ICUs will add either strategy A or strategy B. Thus, the three study arms include usual care, strategy A, and strategy B. Because of variability in study ICUs, we will create pairs matched based on ICU type (medical, surgical) and baseline bundle proportional performance (above and below median) to improve group balance. Within matched pairs, each ICU will be assigned to strategy A or B, and matched pairs will be randomly assigned to one of six wedges which will determine the strategy initiation dates. All hospitals will contribute a minimum of 3 months of data prior to adopting an implementation strategy. By the completion of the 27-month trial, all ICUs will contribute a minimum of 9 months of data with an assigned strategy in place. At trial end, both strategies will be removed but we will continue to follow implementation and clinical outcomes to assess the effect of de-implementation of the strategies. During this time, we will also assess key stakeholders' perceptions of their assigned implementation strategies and how each strategy affected their clinical workload.

We believe the study design is ideal for several reasons. First, the blending of clinical effectiveness and implementation trial design components affords benefits over pursuing either of these lines of research independently (allowing rapid translational gains in bundle uptake, providing more effective implementation strategies, and more useful information for stakeholders).<sup>181</sup> Hybrid Type 3 studies are particularly useful in scenarios, like the ABCDEF bundle, where there is strong "implementation momentum" toward adoption of a

Figure 5. Trial Schematic



clinical intervention but a limited understanding of what strategies most effectively foster adoption into everyday practice.<sup>118</sup> Next, patient-level randomization is unfeasible due to the systems level implementation interventions being tested. Third, the interventions complexity favors those strategies be rolled out sequentially, rather than simultaneously. The stepped wedge ensures robust scientific evaluation, while ensuring optimal conditions for strategy rollout across participating sites.<sup>119</sup> Finally, the stepped wedge design allows an examination of the effect of implementation strategies over time, as there may be important periods of adjustment prior to interventions being fully embedded into the care setting.

**Participants. Hospitals.** The study will take place in three geographically and organizationally separate safety net hospitals: NMC, UIHC, and OSU-WMC. These hospitals serve patients from a diverse array of underserved populations including underrepresented racial groups, the uninsured, and rural populations (**Table 2**). Within these hospitals, we will include 12 ICUs that each admit at least 300 patients requiring MV annually (see **Clinical Trials section** for ICU and MV specific statistics). Patients admitted to these units are managed by intensivists and advanced practice providers specializing in critical care. Nurse-to-patient ratios in the ICUs are usually 1:2 and RTs generally manage 6-8 mechanically ventilated patients per shift. Critical care pharmacists oversee each ICU. **Clinicians.** The implementation strategies being tested will target physicians, advanced practice providers, RNs, RTs, pharmacists, and PT/OTs. These team members, along with ICU/hospital administrators and informational technologists, will also be asked to participate in the activities involved in UH3 Aim 3. **Patients.** We will include all adults treated with MV admitted to a participating ICU. As a pragmatic trial focused on reducing health disparities, we will place no restrictions on age, race, ethnicity, sex, or outcome expectation.

**Table 2. Site Characteristics**

Site, Number Hospital Admits Jan. 2021-Jan. 2022	NMC (N= 66,484)	UIC (N=22,555)	OSU-WMC (N=31,028)
Age > 60	32,828 (49.3%)	10,999 (48.8%)	10,882 (37.6%)
<b>Race</b>			
Black	6,826 (10.3%)	1,394 (6.2%)	3,940 (12.7%)
Asian	863 (1.3%)	301 (1.3%)	583 (1.9%)
American Indian or Alaska Native	579 (0.9%)	61 (0.3%)	Not reported
Native Hawaiian or Other Pacific Islander	201 (0.3%)	24 (0.1%)	11 (0.1%)
Other Race	5,280 (7.9%)	1,453 (6.4%)	4,560 (14.7%)
White	52,735 (79.3%)	19,322 (85.7%)	21,934 (70.7%)
<b>Rurality</b>			
Urban	52,602 (79.1%)	12,197 (54.0%)	Not reported
Rural	7,934 (11.9%)	9,936 (44.1%)	Not reported
Unable to map	5,948 (8.9%)	422 (1.9%)	Not reported
<b>Primary Insurance</b>			
Medicare	9,384 (14.1%)	9,404 (41.7%)	9,989 (32.2%)
Medicaid	3,336 (5.0%)	4,104 (18.2%)	7,732 (24.9%)
Private	7,821 (11.8%)	7,181 (31.8%)	11,914 (38.4%)
Other Insurance/Unknown	45,943 (69.1%)	1,866 (8.3%)	1,482 (4.8%)

**Implementation Strategies.** The trial will include two strategies to increase ABCDEF bundle adoption. The research protocol outlining the specific components of each implementation strategy and how they will be operationalized, implemented, measured, and monitored for fidelity will be finalized by the end of phase 1.

**Real-time Audit and Feedback.** Audit and feedback (A&F) is a well-studied implementation strategy that provides teams a summary of their performance over a specified time period with the goal of changing behavior. A Cochrane Review<sup>120</sup> reported A&F is most effective when used in situations where baseline performance is low (like the ABCDEF bundle), it is provided more than once, and includes both explicit targets and an action plan. While A&F could be delivered in many different formats (written, verbal) and time intervals, the increasing availability of EHR data significantly increases potential to support real-time A&F to affect daily decision-making.<sup>121</sup> Providing electronic A&F to providers organized in teams (like ICUs) is not only a potentially more scalable implementation model but possibly a more effective strategy considering the bundle is delivered by multiple ICU team members who are responsible for the same patients and complex care coordination is required. Use of A&F is specifically responsive to our preliminary study that showed unit level factors influence daily SAT/STB performance more than patient characteristics alone.<sup>68</sup> In addition, the use of A&F was among the top three strategies posed by interprofessional clinicians that are necessary for daily ABCDEF completion.

We plan to provide real-time A&F via a centrally placed visual display (dashboard) in the ICUs randomly assigned to the intervention arm. All providers practicing in the ICU will have access to the dashboard which will be updated in real-time. The dashboard will be created using already established flowsheets, procedures, application reports, activity and navigator records, BestPractice Advisories (BPAs), and tasks within Epic along with the additions already created at the NMC. This dashboard will include the completion status of each of the daily bundle elements by ICU room number (**Figure 6**). The screens will initially alert ICU team members when a patient is eligible to receive a bundle element but has yet to have a safety screen performed by turning yellow. For example, the patient if room 5001 was currently receiving MV but did not have a SBT safety screen documented. A red symbol (bad) will indicate the patient was eligible for the element, passed the

**Figure 6. Example Dashboard**

ICU ROOM NUMBER	A Pain Assessment	B1 SAT	B2 SBT	C Level of Arousal Assessment	D Delirium Assessment	E Early Mobility	F Family Engagement/ Empowerment
5001							
5002							
5003							



initial safety screen, but did not have the element performed. For example, the patient in room 5002 was on MV, passed their SBT safety screen, but did not receive their SBT. A green button (good) will indicate the patient either passed the safety screen and received the element or was not eligible to have the element performed because they did not pass the safety screen. Finally, an X will display in the cases where a patient is not eligible for a particular element (patient not receiving continuously infused sedatives or MV).

**RN Implementation Facilitator.** Our preliminary studies found ICU clinicians indicate that sufficient staffing, effective team communication, and care coordination are keys to successful ABCDEF bundle implementation.<sup>68,86,87,117</sup> We propose a strategy to enhance all three of these goals in the form of a RN bundle implementation facilitator. For the proposed work, the RN facilitator will be trained and come from within current ICU teams (internal facilitation). We chose to use internal (vs. external) facilitators because of their familiarity with site-specific organizational structures, procedures, and clinical policies/processes.

Facilitation is a comprehensive approach in which implementation experts' partner with local staff to support implementation planning and to tailor adoption strategies to local contexts.<sup>122</sup> While facilitation can take many forms, for this trial, we will seek to address the needs identified by ICU clinicians in the following ways. First, the RN will serve as a practical clinical facilitator, acting as extra support to carry out the functions of the ABCDEF bundle. For example, three key areas cited by ICU team members as needing greater support are assisting with early mobility, monitoring patients during SATs/SBTs, and providing increased surveillance immediately post-extubation. Focus group interviews during the UG3 phase, will help guide site-specific areas, where staffing support would lead to enhanced bundle adoption. Second, the RN facilitator will serve as ABCDEF coordinator. For example, while research strongly supports pairing SATs/SBTs, poor coordination prevents many ICUs from reaching this goal. The RN facilitator will also help coordinate daily rounds, ensuring the bundle is discussed and shared goal setting is facilitated. Rather than a visual display of bundle performance, the RN facilitator will provide in-person daily reminders of ABCDEF bundle practices. The RN facilitator will also serve as a champion and coach. As champion, the RN will promote clinician behavior change through motivation, encouragement, and positive reinforcement. As coach, they can facilitate training of the bundle elements for team members, promote high-quality process performance, and build a culture that embraces less sedation, more mobility, and greater family engagement.

Finally, this strategy directly addresses a known barrier to evidence-based care delivery (high nursing workload). Prior research indicates that an adequate number of nurses is indeed necessary to improve bundle compliance in other ICU conditions such as sepsis.<sup>123</sup> Moreover, in a recently published study examining sepsis mortality among Medicare beneficiaries each additional nursing hour per patient day was associated with 3% reduced odds of 60-day mortality, after adjusting for patient characteristics.<sup>124</sup> Extrapolated to the proposed work, the addition of a RN implementation facilitator across an ICU would be expected to increase the number of nursing hours per day among patients receiving MV in a given ICU by 0.5 to 1 hour assuming 8-12 patients on MV per typical unit. Should the RN facilitator prove effective at increasing bundle delivery and/or improving clinical outcomes, this would strengthen the argument for implementing the strategy on a larger scale particularly in under-resourced safety net hospital. Demonstrating RN implementation facilitation effectiveness is also a necessary and critical first step in eventually evaluating the overall cost benefit of this approach.

**Blinding.** Given the nature of the implementation strategies, blinding providers and study Co-Is who work or have study-related responsibilities in the participating ICU to the assigned study arm is not possible. However, all bundle performance and clinical outcome data will be derived from the EHR by local PCORnet data managers who are blinded to the ICUs study arm. This data will be transferred to the study coordinating center and prepared by the study statistician (**Wichman**), who will present data masked by study arm to the investigative team. An independent steering committee will assist in monitoring data collection, study progress, and patient safety.

**Monitoring and Maintaining Intervention Fidelity.** Our strategy to achieve intervention fidelity is grounded in best practice recommendations from the NIH Behavior Change Consortium.<sup>125</sup> Our group has performed multiple clinical trials of complex interventions that required extensive intervention fidelity programs and expect few barriers in this regard. **Delivery of Bundle.** Before the proposed trial, site PIs will identify bundle champions from each participating ICU. Each ICU will have at least one champion from each of the following professions: medicine, nursing, pharmacy, respiratory therapy, and either physical or occupational therapy. Before the trial launches, these champions will undergo standardized training that includes each site's bundle-specific policy and the final research protocol. Champions will also be provided with bundle-related educational resources to use with their staff built for our previous work with the ICU Liberation Collaborative. Retraining will occur on a biannual basis for all units to account for turnover and for ongoing knowledge/practice retention. **Delivery of Implementation Interventions.** Site PIs (Hetland, Krupp, and Gerlach) and clinical research coordinators (CRCs) will monitor implementation fidelity in each participating ICU using a multifaceted, mixed methods strategy. Adherence to core components of the implementation interventions will be regularly monitored by CRCs using direct observation and data extracted from the EHR following a study-developed checklist to ensure that

all units are receiving the same implementation intervention in the manner determined during Phase 1. Exposure to the RN implementation facilitator intervention will be measured using staffing data from each participating ICU to ensure this RN is not counted in regular staffing numbers (free of assigned patient care).

**Evaluation Framework.** We will evaluate key implementation and clinical outcomes using the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework.<sup>126</sup> We chose RE-AIM because it considers both implementation and clinical effectiveness outcomes and addresses maintenance of the interventions over time (**Table 3**). The primary study outcome, and primary implementation endpoint, will be ABCDEF bundle adoption (UH3 Aim 1). Consistent with our prior studies, adoption will be defined as proportional bundle performance (the percentage of eligible elements a patient receives on a given ICU day [“bundle dose”]). The operational definitions and ICU days eligible for each bundle element are provided in the **Clinical Trial Information Form**. Secondary implementation outcomes include acceptability and work intensity (UH3 Aim 3). Acceptability, defined as the extent to which stakeholders believe an intervention or an implementation strategy is agreeable, palatable, or satisfactory,<sup>127</sup> will be measured through online surveys and interviews. Work intensity is defined as the subjectively reported level of mental effort expended in work performed to meet clinician responsibilities as measured by the National Aeronautics and Space Administration Task Load Index (NASA-TLX).<sup>128</sup> Finally, in addition to the clinical effectiveness outcomes in **Table 3**, we will also evaluate potential safety events including reintubation and ICU fall rates. Other outcomes may be added based on the work performed in the UG3 phase.

Table 3. Trial Outcomes Categorized by REAIM Framework

Element	Endpoints	Data Collection
Reach	ICUs and providers (N) participating in trial	Site participation logs
	Eligible patients (N) receiving care in participating ICUs	EHR
Effectiveness	<b>Primary clinical endpoint:</b> Duration of MV	EHR
	<b>Secondary clinical endpoints:</b> ICU, hospital, and 30-day mortality; ICU and hospital length of stay; ICU days with acute brain dysfunction; Discharge disposition, medication, and physical therapy utilization; 30-day hospital readmission	EHR; Social Security Death Index
Adoption	Fidelity of the implementation strategies	Direct observation; Staffing data
Implementation	<b>Primary study outcome (Primary implementation endpoint):</b> Proportional ABCDEF bundle performance	EHR
	<b>Secondary implementation endpoints:</b> Acceptability; Work intensity	Surveys; Interviews
	Safety: Reintubation; ICU fall rates	EHR
Maintenance	Continued ABCDEF bundle performance among patients after clinical trial	EHR

**Data Collection. UH3 Aims 1 and 2.** As a pragmatic clinical trial, all bundle performance and clinical outcome data will be captured via the EHR. Prior to the clinical trial, SAS procs for research dataset retrieval from the three PCORnet datamarts will be tested first at NMC. The SAS extracts will then be distributed to all three sites for quarterly research data reporting following datamart refresh and statistical validation. Query datasets will be transferred employing PCORnet data management protocols and Amazon Web Services S3 transfer utilities to the consolidated UNMC research repository for interim patient safety reviews and statistical analysis.

**UH3 Aim 3.** Work intensity will be measured by the 6-item NASA-TLX which includes physical, mental, temporal demands, performance, effort, and frustration dimensions. The NASA-TLX is a well-studied, valid, and reliable measure<sup>128</sup> that has been used to study clinical work intensity among physicians and ICU nurses including those conducted by Dr. Horner (Co-I).<sup>129-134</sup> The scores for the six items will be averaged and normalized, such that the range of possible clinical work intensity will be 0 (low) to 100 (high). The 6-item NASA-TLX takes less than 1 minute to complete. We plan to administer the NASA-TLX to all ICU team members who work in a participating ICU via an online survey (delivered via REDCap). Participants who work dayshift, the time both implementation strategies would be simultaneously in place, will be asked to complete the survey at the end of their workday, four times a month during the clinical trial. The days of survey administration will be randomly assigned by the study statistician and passed along to site CRCs who will notify staff of the need to complete the survey on the days assigned.

Upon trial completion, all ICU team members, administrators, and IT specialists who worked in a participating ICU during the trial will be invited to participate in an on-line survey (delivered via REDCap). This survey will include the 4-item Acceptability of Intervention Measure (AIM).<sup>135</sup> The AIM was specifically developed to meet the need for a reliable, valid, and pragmatic measure of the implementation outcome acceptability. The four AIM questions are: (1) XXX meets my approval, 2) XXX is appealing to me, 3) I like XXX, and 4) I welcome XXX. Responses range from 1=completely disagree to 5=completely agree. The AIM has strong psychometric properties.<sup>165</sup> Specifically, the AIM demonstrates content validity, discriminant content validity, reliability, structural validity, structural invariance, known-groups validity, and responsiveness to change. Finally, a purposeful sample of ICU clinicians (n=60) will be invited to participate in interviews led by Drs Kim, Hetland, and Krupp (Co-Is). Participants will be selected based on trial arm and responses to the acceptability measure (representing low, middle, and high acceptability) as well as from each profession group. Participants will be asked about overall perceptions and experiences on implementation strategy as well as barriers and facilitators specific to CFIR domains and constructs (see guide in **Clinical Trials Form**).

**Study Design, Sample Size, and Power.** This study utilizes a stepped wedge, hybrid type-III implementation trial that mimics the design used in the INPUT trial.<sup>136</sup> This design is two, six-cluster, 9 time period stepped wedges with a two-time period transition (Strategies A and B) run simultaneously (**Figure 5**). Participating ICUs average 20 to 25 patients on invasive MV per month representing an estimated 6400 to 8100 patients over the 27-month length of the study. Sample size was established using the swCRTdesign package<sup>137</sup> in R version 4.0.1 (R Core Team, 2020) and a desire to detect a difference in proportions of 0.25 between the strategies, or each strategy vs control. The sample size analysis is based on a stepped wedge design with 6 steps, 2 ICUs per step, 2 time periods used to get strategies A and B implemented and no extra time periods. Time periods are 3 months in length. The following baseline and variability assumptions were made: the marginal utilization rate prior to implementation of either strategy A or B will be 0.45, the standard deviation of the random cluster effect is 0.15, time is treated as a fixed effect, and the intra-cluster correlation is 0.15. The swCRTdesign package uses the combined variability based on the assumed marginal proportions to compute variability due to error when the outcome is binary. Utilizing varying sample sizes ranging from 60 to 75 subjects per ICU per time period achieves > 95% power using a significance level of 0.01 (Bonferroni adjusted to be conservative). Twelve clusters are sufficient to detect a difference in proportion between any of the strategy combinations and control with >80% power if the observed effect is greater than or equal to 12%. The sample size analysis was repeated for being able to detect a minimum mean difference of 1.5 days on MV between any strategy and control, or between the two strategies using a standard deviation for the random cluster effect of 1.0, an ICC of 0.15, and a residual error of 3.4. At a conservative significance level of 0.01 for alpha, the current design achieves 87.7% power to detect a 1.5 day difference.

**Data Cleaning and Preliminary Analysis.** Categorical data will be tabulated to ensure coding is consistent (i.e., Yes, Y, yes). Box plots and/or histograms will be used to evaluate distributions of continuous variables, and to identify possible outliers. For survey/clinical test based quantitative outcomes, values will be compared to ensure all values lay between the minimum and maximum scores/between the limits of detection, respectively. Observations falling outside of possible values will be investigated to determine the correct value. If the correct value cannot be determined, the value will be removed. Values identified as potential outliers will be investigated, if they are determined to be correct, the original value will be retained. Demographic variables and primary outcomes of individuals for each time point will be summarized using descriptive statistics for each ICU and Hospital separately. Continuous variables will be summarized by mean and standard deviation or median and inter-quartile range, as appropriate. Discrete variables will be summarized as count and proportion. Independent t-tests (or appropriate non-parametric tests) will be used to determine if there are pre-existing differences in the outcome variables at baseline. Unless otherwise specified, the significance level for all tests will be 0.05.

**Social Determinants of Health.** The CDC defines 5 key areas of SDOH: Healthcare Access and Quality; Education Access and Quality; Social and Community Context; Economic Stability; and Neighborhood and Built Environment. SDOH variables that can be reasonably addressed in this study are sex, age, race, ethnicity, insurance status, rurality, and area deprivation index (Zip Code). Summary statistics for all primary and secondary outcomes under the control, strategy A, and B conditions will be computed at the hospital (different localities) and aggregate levels, for each level of each SDOH (age will be binned by decade, i.e., 18-19, 20-29, 30-39, etc). This analysis will be used to look for discernible patterns in adoption or clinical outcomes that may be linked to SDOH. These summaries will also be utilized to inform which SDOH variables may have interacting effects on the outcomes in UH3 Aims 1 and 2.

**Analyses by Aim. UH3 Aim 1.** The analysis plan will be conducted on two levels: modified (mITT) and true intention to treat (ITT). Since this study is focused on the adoption of the ABCDEF bundle on MV patients by ICUs, patients that were placed on MV prior to admission to the ICU or whose MV straddles transition points in the study will be excluded from the primary analysis (mITT). The ITT secondary analysis will include those patients that were on MV prior to ICU admission and those that straddle transition points. Individual-level generalized linear mixed models with random effects for hospital and ICU within hospital and fixed effects for both calendar time and exposure time will be utilized to quantify group differences in the primary outcome of proportional bundle performance.<sup>138,139</sup> The GLMM will have the following form (excluding covariates for clarity):  $g(E[Y_{ijtkl} | \gamma_{0i}, u_{0ij}]) = \beta_0 + \gamma_{0i} + u_{0ij} + \beta_t + E_{ijtk} + \delta_k I(\text{strategy}) + e_{ijtkl}$  where  $\beta_0$  is the intercept;  $\beta_t$  is the fixed effect of calendar time, t;  $E_{ijtk}$  is the fixed effect of exposure time associated with calendar time; t for the k<sup>th</sup> strategy, the j<sup>th</sup> ICU in the i<sup>th</sup> hospital;  $\delta_k$  is the effect of strategy k;  $\gamma_{0i}$  is the hospital specific random intercept;  $u_{0ij}$  is the ICU specific random intercept; and  $e_{ijtkl}$  is the random error. The random components  $\gamma_{0i}$ ,  $u_{0ij}$ , and  $e_{ijtk}$  are all assumed to be normally distributed with mean 0 and variance  $\sigma_\gamma^2$ ,  $\sigma_u^2$ , and  $\sigma_e^2$ , respectively. Additionally,  $\gamma_{0i}$ ,  $u_{0ij}$ , and  $e_{ijtk}$  are assumed to be mutually independent. Calendar and exposure time can be entered into the model either as categorical or as continuous variables. When time is entered as a

continuous variable,  $\partial_k$  represents a time averaged effect of strategy. For the primary outcome of adoption of the ABCDEF bundle,  $g(\cdot)$  is the logit link function.

There are three primary comparisons of interest: strategy A vs control; strategy B vs control; and strategy A vs strategy B. The first two differences will determine the effect of real time A&F and RN over standard practice, respectively; the third difference will determine if either strategy A or B is better. Type I error rate will be controlled at 0.05 by utilizing the Holm-Bonferroni adjustment for multiple comparisons. Analyses will be adjusted for patient level covariates that were present prior to ICU admission: **sex, age, race**, insurance status, rurality, comorbidity score, LOS in hospital prior to ICU admission, LOS in ICU prior to MV, and duration of MV prior to ICU admission. We are specifically interested in whether SDOH modifies the effect of the intervention on bundle performance. As such, we will specifically examine SDOH-intervention interaction terms to understand the extent to which a given SDOH may change the effect of specific interventions on proportional performance of the ABCDE bundle.

**UH3 Aim 2.** Individual level clinical outcomes will be analyzed utilizing the same model outlined for Aim 1, with the exception that the link function will change based on the nature of the outcome being modelled (e.g., continuous outcomes will utilize the identity link and count data may use the logit or log link dependent on the assumed distribution). Covariates identified in the Aim 1 analysis plan will be considered in all Aim 2 analyses. Biologically reasonable interactions will be considered, but only retained in models if the p-value is  $\leq 0.10$ .

**UH3 Aim 3.** We will use summary statistics to describe acceptability scores for each implementation strategy. Bivariate analysis (t-test, ANOVA) will be used to compare acceptability score among different types of implementation strategies. Individual work intensity (NASA-TLX scores, 0-100) will be aggregated by each unit, and averaged weekly to assess trends over time. We will then correlate work intensity score by acceptability score and adoption rate using Pearson or Spearman correlation analysis. Since the provider responses are correlated within a unit, we will use linear mixed models to examine the association between work intensity and implementation outcomes (acceptability, adoption), controlling for provider characteristics and work-system factors. For interview analysis, following Lam et al's<sup>140</sup> approach we will conduct a template analysis of interview transcripts to identify themes describing facilitators and barriers of the proposed implementation strategies related to CFIR constructs. Using the CFIR coding as a template, we will conduct a hierarchical and structural coding to meet the proposed study's special needs.<sup>141</sup> Multiple coders will review and discuss the CFIR coding definition, inclusion and exclusion criteria to build a collective understanding of the codes. Each coder will independently code the transcript and meet regularly to review coding consistency and discuss problematic constructs. The coding team will meet after all the coding to discuss preliminary themes to reach a consensus. All coding and analysis will be conducted in NVivo 12. Finally, quantitative and qualitative analysis results will be synthesized to gain deep understanding of stakeholder's perspectives on acceptability and staff work intensity.

**Missing Data.** ICUs are controlled environments where documentation of actions taken on a patients' behalf are critical to satisfactory outcomes; therefore, we do not anticipate having missing observations in the variables for the analyses described in Aims 1 and 2. However, for individual patients missing data that will not allow for the determination of whether a bundle element was performed (e.g., on MV but no SBT documented) will be treated as if that bundle element was not performed. Every effort will be made to fill in missing patient level covariate data from secondary and tertiary records (outside the EHR). If the data is not recoverable, analyses will be run using both list-wise deletion (reduced data set) and multiple imputation. For multiple imputation the mice (multivariate imputation by chained equations) and brms (Bayesian Regression Models using STAN) packages will be utilized. A comparison of the results of the two methods will be tabulated; any discrepancies between the two models will be investigated to see if there was any systematic or characteristic that defines the missingness.

**Potential Challenges and Alternative Approaches.** Our experienced team has successfully completed multiple ICU clinical trials using complex interventions and mixed methods. However, some potential challenges with planned responses include the following. First, nurses are experiencing high levels of burnout. We believe the facilitator may mitigate this burnout, however, hiring may prove challenging. We have already adjusted by making facilitators only required for ½ of the ICUs. We will be prepared to modify the role to allow for reduced work hours, alternatively trained providers (nursing assistants) as well as consider remote facilitation options. Second, all three hospitals are committed to implementing the bundle and proposed implementation strategies (see **Letters of Support**). However, if a site decided to opt-out of study participation our ICU Liberation Collaborative connection will allow the opportunity to add additional hospitals/ICUs. Finally, the project is occurring during a pandemic. As such, there may be changes in patient populations as well as practice patterns. We will work with sites to monitor for new COVID surges as well as any changes in policy/procedure. Key changes will be accounted for analytically for Aims 1 and 2 and potential changes in policy at individual ICUs will be addressed using an additional fixed period effect.

**UH3 Timeline and Core Milestones.** A detailed chart showing UH3 core milestones and key project management activities are included in the **PHS Human Subjects and Clinical Trial Information** form.

## Resource Sharing Plan

The research team is committed to following the NIH's guidelines for data sharing that is outlined on the website to further the goals of increased rigor and transparency in science. Our primary goal is to make the most of the rich and important data that we collect over the course of this study.

In response to this goal, we will develop a data repository that will be made widely available to qualified investigators. We will enact all measures to safeguard the privacy of Hospitals, ICUs, ICU team members, and patients. Human data will be de-identified and transferred appropriately in compliance with federal regulations. Upon publication of the primary manuscript, the study database will be made available to the public upon request through a data warehouse mechanism and appropriate data use agreement (e.g., privacy and confidentiality measures, research use, appropriate acknowledgements, and restrictions on sharing) to pursue other analyses and hypothesis generation indefinitely. In addition to appropriate data sharing, our study will be registered prior to initiation on [CliniclTrials.gov](https://clinicaltrials.gov), with clear identification of study procedures and primary/secondary outcomes.

**SUPPLEMENTARY  
MATERIAL**