Trials

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Behavioral Economic and Staffing Strategies To Increase Adoption of the ABCDEF Bundle in the Intensive Care Unit (BEST ICU): study protocol for a multi-site stepped-wedge cluster randomized controlled trial in the USA

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Abstract

Background Despite its proven safety and effectiveness at liberation from mechanical ventilation, ABCDEF (Assess, prevent, and manage pain; Both spontaneous awakening and breathing trials; Choice of analgesia/sedation; Delirium: assess, prevent, and manage; Early mobility/exercise; and Family engagement/empowerment) bundle performance in everyday intensive care unit (ICU) practice remains disappointingly low. This evidence-to-practice gap significantly contributes to the excessively high morbidity, mortality, costs, and disparities associated with current critical care delivery. This study will evaluate the effects of two discrete, behavioral economic, and implementation science-based strategies on ABCDEF bundle adoption and patient-centered outcomes.

Methods The Behavioral Economic and Staffing Strategies To Increase Adoption of the ABCDEF Bundle in the ICU (BEST-ICU) study is a three-arm pragmatic, stepped-wedged, cluster-randomized hybrid type 3 effectiveness-implementation trial aimed at detecting superiority of real-time audit and feedback (A&F) via an electronic dashboard versus registered nurse (RN) implementation facilitation on proportional ABCDEF bundle performance (primary implementation outcome), complete ABCDEF bundle performance (secondary outcome), and duration of invasive mechanical ventilation (secondary outcome). The study will include 8100 patients admitted to 12 ICUs from 3 discrete safety net hospitals. Patients included will be ≥ 19 years old, admitted to a participating ICU for at least 24 h, and have received invasive mechanical ventilation during their ICU stay. All bundle performance and clinical outcome data on patients will be captured via institutional electronic health records (EHR). During the 27-month study, participating ICUs will be randomly assigned to either real-time A&F or an RN implementation facilitation using a two-step, stratified randomization process. At the study's end, both strategies will be removed (i.e., unless ICUs independently decide to continue the strategy), while implementation and clinical outcomes are followed for an additional 3 months,

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and key stakeholders' experiences with, and perspectives of, real-time A&F and RN implementation facilitation are explored.

Discussion Using a novel study design while building upon currently available EHR technology and established patient-centered outcomes research network capability, the BEST ICU study will be the first translational research trial specifically aimed at developing and testing theory-based, clinician-informed, pragmatic, and potentially sustainable ABCDEF bundle implementation strategies.

Trial registration ClinicalTrials.gov NCT 06184945. Registered on December 13, 2023

Keywords Audit and feedback, Nurse facilitation, ABCDEF bundle, Mechanical ventilation, Intensive care unit, Critical care unit, Implementation science, Stepped wedge, Electronic health record

Introduction

Background and rationale {6a}

Each year, over five million Americans are admitted to ICUs, and over one-quarter of all ICU beds in the USA are occupied daily by patients receiving invasive mechanical ventilation (iMV), defined as having either an endotracheal tube or a tracheostomy in place and receiving all oxygen via a ventilator [1–4]. While ICU survival rates have improved, this survival often comes with heavy personal costs [5]. ICU patients commonly experience symptoms that cause acute suffering and have long-lasting effects [6, 7]. Pain, experienced by ≥ 70% of patients, is distressing, often undertreated, and frequently present with routine ICU activities (e.g., tracheal suctioning, turning) and at rest [8–10]. Delirium, occurring in up to 80% of patients requiring iMV [11, 12], is associated with hospital-acquired complications, prolonged iMV, and need for long-term care facilities [13]. Lastly, ICU-acquired weakness, often caused by ICU medications and bed rest, occurs in up to 50% of critically ill patients [14–16]. The effects of ICU pain, delirium, and weakness extend beyond hospitalization, being consistently associated with functional decline, neurocognitive impairment, and mortality [6, 16–23].

Highly efficacious and safe interventions for iMV liberation, symptom management, and mobility exist. In 2018, the Society of Critical Care Medicine (SCCM) released its clinical practice guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) in adult ICU patients [7]. Current and past PADIS guidelines recommend several evidence-based interventions to improve patient outcomes [6, 7]. These interventions include the following: (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), (3) target-based sedation protocols and/or an analgesia-based sedation approach, (4) avoiding benzodiazepines, and (5) performing early and frequent mobilization. Additional benefits are accrued when SATs are combined with iMV discontinuation protocols (spontaneous breathing trials or SBTs) [24–26]. The ABCDEF bundle (Fig. 1) is an evidence-based, multicomponent, interprofessional approach to implementing the PADIS guidelines [27–29]. 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.

Despite bundle efficacy, multiple studies show that the evidence-based interventions contained in the ABCDEF bundle are infrequently used in ICU practice [30–35]. For example, by the end of the Society of Critical Care Medicine's ICU Liberation Collaborative, the proportion of patients receiving complete bundle performance was only 12%. Furthermore, only 59% of all bundle elements were completed by the study's end [35]. Finally, ongoing implementation gaps in ABCDEF care delivery may further exacerbate healthcare disparities in critical care outcomes, as adults with known health disparities experience

Fig. 1 The ABCDEF bundle. Abbreviations: SAT, Spontaneous Awakening Trial; SBT, Spontaneous Breathing Trial

worse quality of life and employment outcomes after critical illness compared to whites [36–38]. For example, 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 [36, 39]. Data also indicate racial disparities in post-intensive care syndrome, quality of life, and employment outcomes after a critical illness [37, 38].

Overcoming ABCDEF implementation gaps requires a better understanding of strategies to enhance uptake. Clinicians cite the amount of work and interprofessional care coordination needed to implement the bundle effectively as an implementation challenge [40–48]. Despite dozens of studies documenting the association between nurse staffing and patient outcomes in the acute care setting [49], to our knowledge, no randomized controlled trials (RCTs) have evaluated the effectiveness of adding a registered nurse (RN) implementation facilitator to the ICU team in improving ABCDEF bundle performance [46, 50].

Clinicians, furthermore, have reported a desire to have performance data routinely available through audits and feedback [51], an approach rooted in behavioral economics. Researchers increasingly use behavioral economic interventions delivered via EHR systems to harness the predictable ways human judgment is biased to improve decisions [52]. These interventions, often known as "nudges," reshape how options are presented to decision-makers to optimize their choices [53]. One systematic review found that the most studied, effective, and least restrictive nudge in healthcare was framing information for clinicians through peer comparison and/or audit and feedback (A&F) [54]. Few studies have examined the effect behavioral economic interventions have on ICU decision-making, and none is specific to ABCDEF bundle adoption [55, 56].

Objectives {7}

The overarching aim of the BEST ICU trial is to support the "real-world" assessment of two discrete strategies, real-time audit via an electronic dashboard and feedback and RN implementation facilitation, to increase the adoption and equitable delivery of the ABCDEF bundle in ICUs caring for critically ill patients. All primary and secondary outcomes refer to the patients' index ICU stay. Simultaneously, we will assess the effects of the intervention on ICU providers' attitudes and perceptions of work intensity.

Primary objectives

The primary implementation aim (Objective 1a) is to compare the effectiveness of real-time A&F through an electronic dashboard and RN implementation facilitation on proportional ABCDEF bundle performance (primary study outcome) among patients receiving iMV. The trial's primary clinical aim (Objective 1b) is to compare the effectiveness of real-time A&F and RN implementation facilitation on the duration of iMV (Table 1).

Secondary objectives

The secondary objectives are as follows:

2a. Compare the effectiveness of real-time A&F and RN implementation facilitation on complete ABCDEF bundle performance.
2b. Compare the effectiveness of real-time A&F and RN implementation facilitation on additional patient-centered outcomes (e.g., new tracheostomy placement, advanced noninvasive respiratory therapy [ANRT], length of stay [LOS]). Additional outcomes are provided in Table 1.
3. The third study objective is to identify and describe key stakeholders' experiences with, and perspectives of, real-time A&F and RN implementation facilitation. We will accomplish this objective with four sub-aims.

a Compare the effects of real-time A&F and RN implementation facilitation on work intensity.
b Compare the effects of real-time A&F and RN implementation facilitation on work intensity.
c Assess the association of work intensity with acceptability and proportional bundle performance.
d Assess providers' perspectives on barriers and facilitators to adopting real-time A&F and RN implementation facilitation.

Overall, we expect the study 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 racial/ethnic healthcare disparities and ultimately improve the care and outcomes of millions of critically ill adults annually.

Trial design {8}

The BEST ICU study is a three-arm, pragmatic, stepped-wedge, cluster-randomized hybrid type 3 effectiveness-implementation trial that will be implemented over 33 months (3 months devoted to start-up activities) across 3 academic medical centers and 12 ICUs. Figure 2 provides a diagram of the trial.

Table 1 Outcomes for study objectives 1 and 2, including measure timing and outcome definitions

	Baseline (hospital & ICU admission)	Daily while in ICU	Hospital discharge	Posthospital discharge — 30 days	Outcome measure definition
Primary implementation objective					
Proportional ABCDEF bundle performance		**X**			The proportion of ABCDEF bundle elements received on an ICU day (see below for individual bundle elements) Numerator: No. of individual bundle elements received Denominator: Total no. of eligible bundle elements
Primary clinical objective					
Duration of invasive mechanical ventilation		**X**			Duration (in hours): extubation time—intubation time. In the case of multiple intubation/extubation episodes, we will sum the duration of separate mechanical ventilation episodes
Secondary implementation objective					
Complete ABCDEF bundle performance					An ICU day in which every eligible element of the bundle was performed (i.e., 100% of the eligible bundle elements completed versus anything less, yes/no)
Individual ABCDEF bundle element performance					
A: Pain		**X**			Frequency of compliance of bundle element A — pain assessment Numerator: No. of eligible patient days in the ICU with ≥ 6 pain assessments using a valid and reliable instrument (i.e., numeric rating scale, Behavioral Pain Scale, [57], Critical Care Pain Observation Tool [58, 59], Defense and Veterans Pain Rating Scale [60], Pain Assessment in Advanced Dementia [61], or numerical rating scale [62]. Pain assessments are part of the standard nursing assessment and documentation procedures in each participating ICU Denominator: No. of days in the ICU
B1: Spontaneous Awakening Trial		**X**			Frequency of compliance of bundle element B1 — Spontaneous Awakening Trial Numerator: No. of eligible patient days a patient has a SAT outcome value of pass Denominator: No. of days in the ICU when receiving continuously infused analgesic/sedative medications
B2: Spontaneous Breathing Trial		**X**			Frequency of compliance of bundle element B2 — Spontaneous Breathing Trial Numerator: No. of eligible patient days a patient has a SBT outcome value of pass. The SBT qualifies when there is evidence in the reduction of mechanical ventilation support with exception of 5 to 8 cm of H2O of pressure support or < 6 of PEEP Denominator: No. of days in the ICU when receiving mechanical ventilation

Table 1 (continued)

	Baseline (hospital & ICU admission)	Daily while in ICU	Hospital discharge	Posthospital discharge — 30 days	Outcome measure definition
C: Sedation assessments		**X**			Frequency of compliance of bundle element C — sedation assessment Numerator: No. of eligible patient days in the ICU with ≥ 6 agitation-sedation assessments using a valid and reliable instrument (i.e., Richmond Agitation-Sedation Scale [63] or Sedation-Agitation Scale [64]. Sedation assessments are part of the standard nursing assessment and documentation procedures in each participating ICU Denominator: No. of days in the ICU
D: Delirium assessments		**X**			Frequency of compliance of bundle element D — sedation assessment Numerator: No. of eligible patient days in the ICU with ≥ 2 delirium assessments using a valid and reliable instrument (i.e., Confusion Assessment Method for the ICU [12], the Intensive Care Delirium Screening Checklist [65], or the Delirium Observation Screening Scale [66]. Delirium assessments are part of the standard nursing assessment and documentation procedures in each participating ICU Denominator: No. of days in the ICU
E: Early mobility		**X**			Frequency of compliance of bundle element E — early mobility/exercise Numerator: No. of eligible patient days that mobility activities were higher than active range of motion (i.e., dangling at edge of bed, standing at side of bed, walking to bedside chair, marching in place, walking in room or hall). Qualifying mobility activities are recorded as part of standard nursing and physical therapist care in each participating ICU Denominator: No. of days in the ICU
F: Family engagement		**X**			Frequency of compliance of bundle element F — family engagement/empowerment Numerator: No. of eligible patient days that a family member/significant other was educated on the ABCDEF bundle and/or participated in at least one of the following: rounds, conference, plan of care, or ABCDEF bundle-related care. Qualifying family engagement activities are recorded as part of standard nursing care in each participating ICU Denominator: No. of eligible patient days in the ICU
Secondary clinical objective					
New tracheostomy placement		**X**	**X**		We will identify incident tracheostomy events using EHR lines/devices data and CPT codes (see **Supplement Table 2** for relevant codes)

Table 1 (continued)

	Baseline (hospital & ICU admission)	Daily while in ICU	Hospital discharge	Posthospital discharge — 30 days	Outcome measure definition
Advanced noninvasive respiratory therapy (ANRT)	**X**	**X**			We will monitor for ANRT using BiLevel Positive Pressure Ventilation (BiPaP) or high-flow oxygen therapy. We will examine specific data elements in the EHR relevant to ANRT. This may include the following: Clinical orders for the initiation of BiPaP or high-flow oxygen therapy ≥ 20L/min Respiratory therapy logs of pressure setting management and/or oxygen deliver device Ventilator settings and parameters recorded over time
ANRT duration	X	**X**			Duration (in hours) = ANRT initiation time—ANRT termination time. In the case of multiple ANRT episodes, we will sum the duration of separate ANRT episodes
ICU mortality		**X**			A death event that is recorded in the EHR that occurred after index ICU admission and prior to the index ICU discharge date and time
Hospital mortality		**X**	**X**		A death event that is recorded in the EHR that occurred after index ICU admission and before discharge from the hospital on the index hospital stay
30-day mortality		**X**	**X**	**X**	A death event that is recorded in the EHR that occurs within 30 days of the date of hospital discharge from the index hospital stay
ICU length of stay	**X**	**X**	**X**		Date and time of ICU discharge minus the date and time of ICU admission. Each ICU stay will be recorded as unique ICU stays as a unique ICU encounter
Hospital length of stay	**X**	**X**	**X**		Date and time of hospital discharge minus the date and time of first encounter during the hospital encounter
ICU days with acute brain dysfunction (delirium or coma)	**X**	**X**			A delirious day would include a 24-h period with at least one CAM-ICU that is measured as positive. The total would include the total number of days for which CAM-ICU is measured to be positive. ICU coma days: We will record any day for which patients exhibit level of arousal scores consistent with coma (*RASS* −4 or −5, SAS score of 1 or 2) and add the total number of coma days throughout any given ICU stay and across all ICU stays within a hospitalization
Physical restraint use	**X**	**X**			Physical restraint status codes will be identified using the ICD-10-CM code Z78.1 "physical restraint status" [67]
Daily opioid dose	**X**	**X**	**X**		Daily morphine milligram equivalent (MME) for patients while in the ICU. We will use the formula as follows: Strength per unit × (number of units/days supply) × MME conversion factor = MME/day. MME dosing is derived from Nielson S. et al.'s synthesis of oral morphine equivalents for opioid utilization studies (see **Supplement Table 3**) [68, 69]

Table 1 (continued)

	Baseline (hospital & ICU admission)	Daily while in ICU	Hospital discharge	Posthospital discharge — 30 days	Outcome measure definition
Total opioid dose	X	X	X		Total MME for patients while in the ICU. We will use the formula as follows: Strength per unit × (number of units) × MME conversion factor = total MME
Daily benzodiazepine dose	X	X	X		Daily diazepam equivalents (DE) for patients while in the ICU. We will use the formula as follows: Strength per unit × (number of units/days supply) × DE conversion factor = MME/day. DE dosing is derived from benzo.org.uk/bzequiv.html
Total benzodiazepine dose	X	X	X		Total DE for patients while in the ICU. We will use the formula as follows: Strength per unit × (number of units) × DE conversion factor = total DE
Daily sedative/hypnotic use	X	X	X		The proportion of days received any dose of a sedative/hypnotic medication. List of medications is available in **Supplement Table 4**
Daily antipsychotic use	X	X	X		The proportion of days received any dose of an antipsychotic medication. List of antipsychotic medications is available in **Supplement Table 5**
Discharge disposition			X		We will review hospital discharge destination coded as home, home with home health, short-term skilled nursing facility, long-term nursing facility, acute rehabilitation hospital, long-term acute care hospital, hospice, acute care hospital, and death
ICU readmission			X		At least one return to the ICU within the same hospitalization following discharge from the index ICU visit
Physical therapy use at hospital discharge			X		We will collect data regarding physical therapy ordered at the time of hospital discharge if discharged to home
30-day hospital readmission				X	At least one same-hospital readmission within 30 days of discharge from the hospital
ICU days with significant pain		X			The proportion of ICU days with at least one episode of significant pain. Significant pain is defined if any of the below are documented: NRS: A score of > 6 will be considered significant pain CPOT: A score > 2 will be considered significant pain BPS: A score > 5 will be considered significant pain DVPRS: A score > 4 will be considered significant pain PAINAD: A score > 4 will be considered significant pain
Minimum, maximum, and mean pain scores in the ICU		X			Multiple pain scores are recorded throughout the day. Each day, we will record the minimum and maximum and calculate the mean daily pain score
Minimum, maximum, and mean level of arousal scores in the ICU		X			Multiple level of arousal scores are recorded throughout the day. Each day we will record the minimum and maximum and calculate the mean level of arousal score

Table 1 (continued)

	Baseline (hospital & ICU admission)	Daily while in ICU	Hospital discharge	Posthospital discharge — 30 days	Outcome measure definition
Unplanned extubation		X			We will assess for evidence of extubations that do not follow provider orders for an extubation and/or are charted as unordered
Reintubations within 24 h of extubation		X	X		We will assess evidence of an order for intubation that occurs < 24 h following evidence of extubation or a prior order for extubation. We will additionally supplement this information using evidence of extubation and intubation through the lines, drains, and airways flowsheets from the EHRs
Extrapyramidal side effects			X		We will monitor for evidence of EPS using diagnostic codes that have been used in administrative studies [70]. In addition, the new prescription or order of medications used to treat EPS will be monitored (see **Supplement Table 6**)
ICU days with physical restraint use		X			Physical restraint status codes will be identified using the ICD-10-CM code Z78.1 "physical restraint status" [67]
Hospital-acquired venous thromboembolic disease (DVT or PE)		X	X		We will query for ICD-10-CM codes associated with thromboembolic disease. The codes are consistent with the coding for CMS hospital-acquired conditions [71]. Diagnosis codes must be a secondary diagnosis code/hospital-acquired
Clinically significant falls acquired during hospitalization		X	X		We will record fall and trauma coding consistent with the CMS health-acquired conditions specification for fracture, dislocation, and intracranial injury. Codes within these ranges on the CC/MCC (complication or comorbidity/major complication or comorbidity) list: 800–829, 830–839, 850–854 [71]
New tachyarrhythmia requiring treatment		X	X		We will identify the administration of new antiarrhythmic medications administered in the ICU through medication administration logs and nursing flow. Included antiarrhythmics are in **Supplement Table 7**. Notably, beta-blockers and calcium channel blockers will not be used, given their less specific nature and use for multiple conditions beyond arrhythmia. We will also include treatment via cardioversion as measured through CPT and ICD-9 codes [72]: CPT codes for cardioversion 92960—Cardioversion, elective, electrical conversion of atrial fibrillation or atrial flutter to sinus rhythm, with anesthesia (separate procedure) o 92961—Cardioversion, elective, electrical conversion of atrial fibrillation or atrial flutter to sinus rhythm, without anesthesia (separate procedure) ICD-10 procedure code: 5A2204Z

Table 1 (continued)

	Baseline (hospital & ICU admission)	Daily while in ICU	Hospital discharge	Posthospital discharge — 30 days	Outcome measure definition
Cardiac arrest		X	X		Cardiac arrest will be identified via the documentation of the following documented ICD-10-CM Diagnosis Codes [73–75]: ICD-10-CM codes are as follows: • I46.0: Sudden cardiac arrest, cause unspecified • I46.1: Sudden cardiac death, so described • I46.2: For cardiac arrest due to underlying cardiac condition • I46.8: For cardiac arrest, due to other underlying condition • I46.9: For cardiac arrest, cause unspecified • I47.2: Abnormally rapid ventricular rhythm with aberrant ventricular excitation in excess of 150 beats per minute • I49.0: Ventricular fibrillation and flutter • I49.01: Ventricular fibrillation CPT code 92950—Cardioversion, elective external
Hospital-acquired pressure ulcer		X	X		We will query secondary diagnosis codes to identify the presence of a hospital-acquired ulcer. The codes are consistent with the coding for CMS Hospital Acquired Conditions [71]

Abbreviations: *ICU* Intensive Care Unit, *ABCDEF* Assess, prevent, and manage pain and Delirium - Both spontaneous awakening and breathing trials - Choice of analgesia/sedation; Early mobility/exercise - and Family engagement/empowerment, *SAT* Spontaneous Awakening Trial, *SBT* Spontaneous Breathing Trial, *PEEP* Positive End-Expiratory Pressure, *ANRT* Advanced Non-invasive Respiratory Therapy, *BiPaP* Bi-level Positive Airway Pressure, *MME* Morphine Milligram Equivalents, *DE* Diazepam Equivalents, *NRS* Numeric Rating Scale, *CPOT* Critical Care Pain Observation Tool, *BPS* Behavioral Pain Scale, *DVPRS* Defense and Veterans Pain Rating Scale, *PAINAD* Pain Assessment in Advanced Dementia, *EPS* Extrapyramidal Symptoms, *ICD-CM* International Classification of Diseases, Clinical Modification, *CMS* Centers for Medicare and Medicaid Services, *CC/MCC* Complication or Comorbidity/Major Complication or Comorbidity, *CPT* Current Procedural Terminology

We will randomize 12 unique ICUs across three separate academic safety net hospitals. A cluster is a unique ICU defined by intensive care physicians' and ICU nurses' coordinated care delivery in a geographically co-localized hospital area. There will be six total sequences, with two clusters randomized per sequence. Each period will be 3 months long, with one period between each step. The first two periods will consist of study start-up activities and baseline bundle performance and outcomes data collection. After removing the study-supported implementation strategies, the final period will consist of ongoing bundle performance and outcomes data collection. Invasively mechanically ventilated patients will be enrolled between the second and final periods. We will follow patient outcomes for up to 30 days after hospital discharge.

As part of a hybrid effectiveness-implementation study, we will obtain ICU provider assessments of workload, implementation strategy acceptability, barriers, and facilitators. To achieve this, we will assess the ICU providers' workload intensity throughout all study periods following the start-up period. Through focus group invitations, we will also assess key stakeholders' perceptions of acceptability, barriers, and facilitators during the final period.

Methods: participants, interventions, and outcomes

Study setting {9}

The study will occur in three discrete US medical centers that serve as safety net hospitals for their local, regional, and state communities: the Nebraska Medical Center (NMC), the University of Iowa Hospitals and Clinics (UIHC), and the Ohio State University Wexner Medical Center (OSU-WMC). They also serve as referral centers for patients living in rural areas, a population that experiences significant health disparities and is underrepresented in research. Within these hospitals, we will include 12 ICUs. Patients admitted to the participating ICUs are managed by intensivists and advanced practice providers specializing in critical care. Nurse-to-patient ratios in the ICUs are usually 1:2, and respiratory therapists (RTs) generally manage 6–8 patients who require iMV per shift. Critical care pharmacists oversee each ICU. Each of the ICUs has preexisting policies in place for guiding the ABCDEF bundle.

Eligibility criteria {10}

Eligibility criteria at the cluster (ICU unit) and patient levels are relevant to the first and second study objectives,

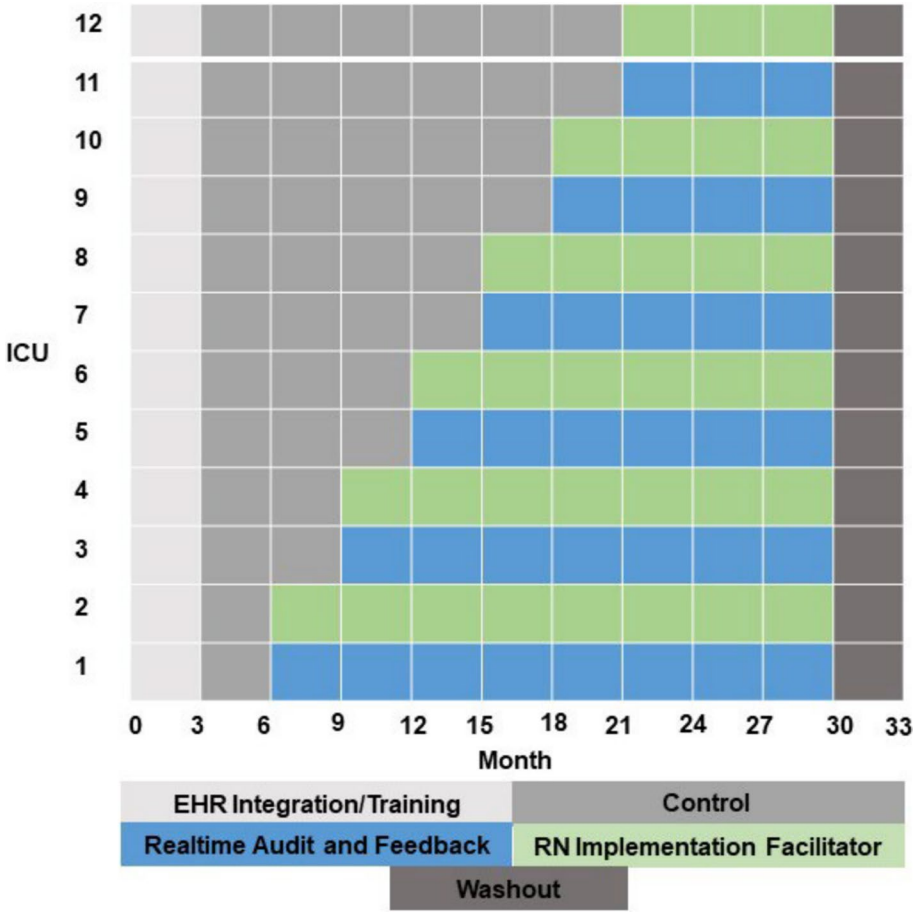

Fig. 2 Trial design. Abbreviations: EHR, electronic health record; RN, registered nurse

and provider eligibility criteria are relevant to the third objective.

Cluster eligibility

We will include ICUs that may care for medical, cardiovascular, surgical, neurological, or neurosurgical patients that are located within one of three geographically and organizationally separate safety net hospitals (i.e., NMC, UIHC, OSU-WMC) that have agreed to participate in the study. ICUs admit at least 300 patients who require iMV annually. We will exclude ICUs that predominantly admit burn patients or non-ICU units (e.g., step-down units).

Patient eligibility

From enrolled ICUs, we will collect preexisting electronic health record (EHR) data collected as part of usual care on patients ≥ 19 years of age who received iMV while in the ICU and had an ICU LOS of at least 24 h. We will exclude patients admitted to the hospital who were receiving chronic long-term iMV and incarcerated individuals.

Provider eligibility

The implementation strategies being tested will target a multidisciplinary team of clinical providers participating in ICU care. Any provider that is included for work intensity surveys or part of a focus group must be age ≥ 19 years and employed full or part-time as an advanced practice nurse, registered nurse, licensed practical nurse, nursing assistant, physician (attending, fellow, resident), respiratory therapist, physical/occupational therapist, and/or pharmacist in a participating ICU.

Informed consent {26a}

We have requested and been granted an institutional review board (IRB) waiver for informed consent for ICU patients and providers based on the premise that the trial meets the Office for Human Research Protections (OHRP) regulations regarding waivers of consent (45 CFR 46.116(f)(3)). Specifically, the research involves no more than minimal risk to the participants (patients and providers are the subjects of data collection procedures which pose minimal risk). Furthermore, the interventions

are designed to increase the uptake of guideline-concordant care. Finally, given the large number of ICU clinicians who practice in the participating ICUs and their frequent turnover, obtaining consent from all ICU clinicians would be impractical. In addition, doing so would increase clinicians' burden without enhancing their research protections. ICU providers, patients, and families will be notified of the study via study information notices placed in visiting areas, patient rooms, work rooms, and break rooms. These notices will describe the study's purpose, interventions, and what the study may mean for ICU patients. Finally, the notices will contain a QR code that links to additional study details.

ICU providers will be given additional bundle and trial information. Before the proposed trial, site principal investigators (PIs) will identify bundle champions from each participating ICU. Each ICU will have at least one trained champion from each of the following professions: medicine, nursing, pharmacy, respiratory therapy, and either physical or occupational therapy, to provide access to bundle-related educational resources to ICUs. Champions will be confirmed biannually to account for turnover and ongoing knowledge/practice needs. Finally, before the online surveys and interviews for the third study objective, we will use an IRB-approved flyer that outlines the following to the healthcare patients or providers in the study (Supplemental Figs. 1 and 2): (1) subject rights, (2) purpose of the study, (3) study tasks or procedures, (4) duration of subject's participation, (5) confidentiality, (6) study contact information, (7) incentives (focus groups only), and (8) study sponsor.

Additional consent provisions {26b}

N/A

Interventions

Explanation for the choice of comparators {6b}

As part of a stepped-wedge cluster randomized trial, both interventions will be compared to each other, as well as with usual care. Usual care at all sites includes standard delivery of the ABCDEF bundle that is guided by existing policies and protocols, with the use of validated measures to assess pain, sedation, and delirium. All sites use EPIC® for their EHR documentation and orders, which include routine documentation of ABCDEF care processes (e.g., SAT).

Intervention description {11a}

The trial will include two strategies to increase ABCDEF bundle adoption: real-time A&F and RN implementation facilitation.

Real-time audit and feedback (A&F)

A&F is a well-studied implementation strategy that provides teams with a performance summary over a specified time to change behavior. A&F is most effective when baseline performance is low (like the ABCDEF bundle), and feedback is provided more than once and includes explicit targets and an action plan [51]. While A&F could be delivered in many formats and time intervals, the increasing availability of EHR data significantly increases the potential to support real-time A&F to affect daily decision-making [76]. Providing electronic A&F to providers organized in teams is a more scalable implementation model and potentially a more effective strategy.

The ABCDEF bundle has been adopted into common EHR software. The SCCM has worked to develop an ICU Liberation (ABCDEF bundle) Implementation Toolkit for critical care providers to measure their practice for quality improvement. For example, 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, best practice advisories, and tasks. Building off this software, study team members created an interactive, dynamic, real-time dashboard in the Epic EHR that tracks process and outcome metrics specific to the ABCDEF bundle.

We will provide real-time A&F via a centrally placed visual display in the ICUs assigned to this intervention arm. All providers practicing in the ICU will have access to the dashboard. This dashboard will include the completion status of each daily bundle element by ICU room number. To ensure consistency among sites, each ICU randomized to the real-time A&F arm will use standardized definitions for each color and symbol on the dashboard provided in Supplement Fig. 3.

RN implementation facilitation

ICU clinicians indicate that sufficient staffing, effective team communication, and care coordination are keys to successful ABCDEF bundle implementation [41, 42, 77, 78]. We will implement a strategy to enhance these goals using an RN ABCDEF bundle implementation facilitator. For the proposed work, the RN implementation facilitator will be trained and will come from within current ICU teams (internal facilitation).

The unit nurse leader(s) from those ICUs randomized to the RN implementation facilitator arm will identify the number of nurses needed to achieve one RN implementation facilitator on the unit for 40 h/week (8 day-shift hours/day, 5 days/week, for the duration of the study). Knowledge specific to the RN implementation facilitator

role will be gained through a combination of existing clinical practice and study-specific training sessions. Facilitators will be as follows: (1) Experienced in the clinical practice setting and identified as a proficient ICU nurse by peers and unit nursing leadership; (2) knowledgeable of ABCDEF bundle evidence and willing to model practices associated with the ABCDEF bundle; (3) familiar with local organizational policies, structures, and context that can affect ABCDEF bundle implementation; and (4) willing to further develop knowledge of implementation science and quality improvement. The RN implementation facilitator role is intentionally designed to be flexible to meet ICU needs in providing ABCDEF bundle interventions.

Criteria for discontinuing or modifying allocated interventions {11b}

There are no pre-specified criteria for discontinuing or modifying the intervention. However, differences by intervention status and over time ("pre-intervention" and "post-intervention") and for the overall trial will be presented in Data Safety Monitoring Board (DSMB) reports for each DSMB meeting along with any reported adverse events (AEs). After reviewing this data after each DSMB meeting, the board may recommend suspending or delaying enrollment in a specific strategy arm. In the scenario that one intervention arm is deemed unsafe, the DSMB may make the decision to stop future randomization to the affected arm and either (a) change the affected arm to the alternative intervention, (b) stop the intervention of the affected arm and return to usual care, or (c) recommend that a specific site stop the intervention.

Strategies to improve adherence to interventions {11c}

For the A&F arm, we will perform routine audits to ensure the dashboard operation and fidelity are met. Research team members will perform a monthly implementation checklist, including direct dashboard observation, to ensure that all patients and bundle components are displayed correctly.

To improve adherence to RN implementation facilitation, we will implement a robust training plan to sustain competencies and core activities. The study team will routinely review unit scheduling and staffing data for the RN facilitator arm to ensure the RN implementation facilitator role is assigned as intended. All RN implementation facilitators will receive an electronic form at 3 and 6 months post-implementation to query their tasks in the participating ICU. Study personnel will monitor implementation fidelity monthly using a study-developed checklist to monitor the core features delivered by the RN implementation facilitator at each site. Furthermore, RN implementation facilitators will meet monthly as part of a learning community to discuss facilitator activities, identify barriers, and receive ongoing education and role mentorship.

Relevant concomitant care permitted or prohibited during the trial {11d}

All control units have site-specific protocols to guide the ABCDEF bundle's delivery. All care in control arms will be at the discretion of the usual care teams in the ICUs. There are no restrictions in care processes or treatments.

Provision for posttrial care {30}

After month 27, study support for both strategies will end, but we will continue to follow implementation and clinical outcomes for an additional three months. The participating ICUs may continue the implementation strategies if they choose, and the study team will track which ICUs stop strategies and which continue of their own accord.

Outcomes {12}

As a hybrid III implementation effectiveness study, we have a primary implementation endpoint and a primary clinical endpoint. The primary implementation endpoint is the proportional ABCDEF bundle performance, and the primary clinical endpoint is the duration of iMV.

The secondary implementation endpoint is the complete ABCDEF bundle performance and individual bundle element performance. The secondary clinical endpoints include a number of key ICU, hospital, and healthcare utilization outcomes, found in Table 1. All primary and secondary outcomes refer to a patient's index ICU stay.

Finally, to assess the perspectives of ICU providers working in the participating ICUs, we will assess the work intensity and acceptability of the intervention, along with a qualitative assessment of barriers and facilitators to adopting the individual strategy adopted in the respective ICU. Table 1 provides the timing of outcomes collection and definitions.

Participant timeline {13}

Beginning on July 1, 2024, ICUs will be enrolled for 27 total months, 24 of which will be either randomized to one of the two implementation strategies or in a pre-intervention control period. We will follow ICUs for three additional months. For eligible patients, we will extract EHR data for their entire hospital stay and obtain follow-up health care utilization and mortality data for up to 30 days following hospital discharge. Eligible providers will receive work intensity surveys throughout all study periods following the start-up period. Furthermore,

after the 27th month, ICU providers will receive a survey to assess the feasibility and adaptability of the study interventions.

Sample size and power {14}

Objectives 1 and 2 (implementation and clinical outcomes)

Participating ICUs average 20–25 patients on iMV per month, representing an estimated 6400 to 8100 patients over the 27-month length of the study. The sample size for Aim 1 and Aim 2 was established using the swCRTdesign package[137] in R version 4.0.1 (R Core Team, 2020) to examine superiority between implementation strategies, 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 six steps, two ICUs per step, two time periods used to get strategies A and B implemented, and no extra time periods. We made the following baseline and variability assumptions: 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 iMV 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.

Objective 3a: Work intensity

The work intensity survey will be conducted on the day shift only, four times per month, throughout the study, regardless of the intervention implementation phase. We anticipate collecting 23,760 total surveys, representing responses from approximately 180 providers across the 12 ICUs. The 180 providers providing responses to the work intensity survey are based on the following: 900 total providers × 50% on day shift × 40% response rate = 180 providers. Having 12 ICUs translates into an average of 15 (180/12 = 15) providers per ICU responding each time the survey is offered. The 23,760 surveys completed are based on 132 time periods (66 each in which an ICU is receiving an implementation intervention or "control [prior to intervention]"), 15 providers per survey, 4 surveys per month, and 3 months per time period ($132 \times 3 \times 4 \times 15 = 23{,}760$).

The sample size for the work intensity analysis was determined under the concept of a parallel, repeated measures, cluster randomized trial comparing mean work intensity between strategy A and strategy B. Twelve (12) ICUs split between strategies (e.g., 6 and 6) with each ICU providing 15 respondents per time period achieve 80% power to discern a difference in mean work intensity of 11.8 units assuming the following: an unadjusted standard deviation of 20 units; correlations of 0.6 and 0.3 for correlation at the respondent and at the ICU levels over time, respectively; respondent level covariates will account for 20% of the unadjusted variance; and an ICC for the primary outcome of 0.05. The sample size was estimated using National Institutes of Health (NIH) Research Methods Resources [79].

Objective 3b: Acceptability

The acceptability survey will be offered to an estimated 900 providers at the end of the active study (study month 28). Based on our assumed 40% response rate, we anticipate responses from 360 providers. The sample size analysis was done under the concept of a parallel, repeated measures, cluster randomized trial comparing mean acceptability between strategy A and strategy B. Twelve (12) ICUs split between strategies (e.g., 6 and 6) with each ICU providing 30 respondents achieve 80% power to discern a difference in mean acceptability of 0.38 units assuming the following: an unadjusted standard deviation of 20 units; correlations of 0.6 and 0.3 for correlation at the respondent and at the ICU levels over time, respectively; respondent level covariates will account for 20% of the unadjusted variance; and an ICC for the primary outcome of 0.05. The sample size analysis was conducted using NIH Research Methods Resources [79].

Objective 3c: Work intensity, acceptability, and bundle adoption

With only 12 pairs of work intensity and acceptability, we can discern a correlation of 0.72 or greater versus no correlation with 80% power when using a significance level of 0.05 and a two-sided alternative hypothesis [80].

Recruitment {15}

We have site PIs identified at all study sites, including representation from physicians, nurses, and pharmacists, which will aid in recruiting and retaining the ICUs and providers. Clinical research coordinators (CRCs) at each site will be responsible for administering ICU surveys

to ICU providers. Patients are enrolled upon meeting patient enrollment criteria via electronic health record data. Given that the interventions under study aim to enhance the application of guideline-directed ICU practice and pose minimal risk, we have received a waiver of consent to participate from ICU providers and patients who receive care within enrolled ICUs. Patients and providers, however, are all informed of the ongoing study procedures and have the ability to access further study information and the ability to make study inquiries and report any perceived study adverse events (see Supplemental Figs. 1 and 2).

Assignment of interventions: allocation

Sequence generation {16a}

The unit of randomization will be the ICU. ICUs will be randomly assigned to either real-time audit and feedback (strategy A) or an RN implementation facilitator (strategy B) utilizing a two-step process: covariate-constrained randomization to assign ICUs to intervention arms and stratified randomization to assign ICUs to steps.

Covariate-constrained randomization involves consideration of all possible randomization schemes, computing balance scores based on a set of constraints, and randomly selecting one scheme out of the subset of schemes whose balance score (i.e., the L2 balance metric) is smaller than a pre-specified criterion [81]. Constraint covariates were chosen as follows: Hospital site, ICU type (e.g., medical), ICU size (no. of beds), and ICU IMV load (percentage of ICU unit patients receiving IMV) to balance potential bundle usage across strategies. The selected covariates yielded 924 (12 choose 6) possible randomization schemes [82].

The biostatistician, independent of the trial statistician, will use a custom R script to allocate ICUs to sequences and treatments. The script will include a seed value to ensure a reproducible allocation scheme.

Concealment mechanism {16b}

The trial statistician will conceal the sequence and intervention allocation until all sites verify that they have all the elements to implement real-time A&F and RN implementation facilitation.

Implementation {16c}

The trial biostatistician will create the randomization schedule. Randomization schemes whose L2 balance scores were less than the 0.1 quantile of all balance scores were deemed to be acceptable. This criterion resulted in 92 acceptable schemes, from which 1 scheme will be randomly selected. Assignment of clusters to sequences will be made by the biostatistician, independent of the trial statistician, following the randomization of sequences.

Assignment of interventions: blinding

Who will be blinded {17a}

As each intervention is visible to the staff within each respective unit, blinding the providers and PIs is impossible. As patients are unlikely to be familiar with the prior ICU environment, it is less likely that patients will be aware of whether their ICU has been assigned to one intervention compared to another. Outcomes will be obtained via the Patient-Centered Outcomes Research Network (PCORnet)-approved common data model at each of the three sites and independently analyzed by a statistician blinded to the ICU, patient, and provider implementation strategy assignments. An unblinded statistician will create an unblinded open report for the purposes of DSMB reports and review.

Procedures for unblinding if needed {17b}

The unblinded statistician will generate reports of pre-specified study outcomes by intervention status and over time ("pre-intervention" and "post-intervention") that will be presented to the DSMB along with any reported AEs directly attributable to either implementation strategy. Following the review of this data, the DSMB may request unblinding to address specific areas of concern in a specific ICU or an implementation strategy.

Data collection and management

Plans for assessment and collection of outcomes {18a}

All patient-level data collected in the BEST ICU study will be obtained at each site from preexisting EHR records supplemented by geocode-linked public domain social determinants of health (SDH) resources the site prepares. Collaborating sites all employ an Epic® EHR and have an approved PCORnet common data model, which is regularly refreshed using structured extracts from the on-site Epic CLARITY® repository. Extracted data are standardized and enhanced with other federal and national data sources, such as the Social Security Death Index. All study data will be extracted from Epic quarterly and formatted to comply with the PCORnet Common Data Model. Tables 1 and 2 list the data collection timeline and study instruments for all outcomes. The Supplement Table 1 includes all additional demographic and clinical data collected.

Plans to promote participant retention and complete follow-up {18b}

We have site PIs identified at all study sites, including representation from physicians, nurses, and pharmacists, which will aid in recruiting and retaining the ICUs and providers. We do not anticipate patient retention and follow-up issues, as all data will be gathered from within

Table 2 Outcomes for study objective 3, including measure collection schedule and outcome definitions

Measures	Four times per month during months 4 through 30	Conclusion of implementation strategy (after month 30)	Measure description
Implementation measures			
Work Intensity	X		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 [83] that has been used to study clinical work intensity among physicians and ICU nurses [84–89]. 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 min to complete
Acceptability		X	All eligible ICU providers who worked in a participating ICU during the trial will be invited to participate in an online survey. This survey will include the 4-item acceptability of intervention measure (AIM) [90]. 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 as follows (Where XXX refers to the intervention experienced by the provider): (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. Specifically, the AIM demonstrates content validity, discriminant content validity, reliability, structural validity, structural invariance, known-groups validity, and responsiveness to change
Focus group interviews		X	A purposeful sample of 60 ICU providers will be invited to participate in focus group. Participants will be selected based on the trial arm and responses to the acceptability measure (representing low, middle, and high acceptability) as well as from each professional 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

the EHR based on care as delivered. We have worked to increase survey responses (e.g., workload intensity) by intentionally designing a very brief instrument that can be completed in a few minutes. Furthermore, we will limit the frequency of data collection related to work intensity to four times per month (Table 3).

Data management {19}

Data will be aggregated by site technical teams into the approved PCORnet common data model employing their usual operational protocols, including removal of all PHI other than actual dates and 5-digit zip codes. The coordinating center will prepare SAS queries for the BEST data extraction, coordinate data management activities, and arrange for software to be employed by each site for maintenance of their PCORNET_TRIAL tables, which will maintain the registry of all participating ICUs, ICU patients, and hospital encounter data that will be collected and analyzed for the project. The queries will automate ICU patient enrollment using computational inclusion and exclusion criteria and ensure the collection of all EHR data specified in the study protocol. Wisconsin Area Deprivation Index, Social Vulnerability Index, and Rural–Urban Commuting Area Codes reference tables and software will be supplied by the coordinating center to participating sites to enable data element computation using zip code geocoding maintained solely at each site.

The SAS queries will be transferred to the three performance sites, where they will be executed by PCORnet technical staff. Query results with all study data will be transferred by sFTP protocols to secure AWS S3 staging buckets hosted at the study coordinating center. Once uploaded to the AWS enclave, data content validation and compliance with security protocols will be confirmed by coordinating center personnel, and the data will be aggregated into an AWS secure repository where reformatting

Table 3 SPIRIT diagram for BEST-ICU Trial, a stepped-wedge cluster randomized trial

											Close Out
	Site Selection	Site Allocation	Control	Intervention Implementation						Washout	
Timepoints	**Pre-trial**	**Initiation**	**Step 0**	**Step 1**	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**	**Step 7**	
Screening of ICUs for eligibility	X										
Allocation of ICUs for the trial		X									
Screening patients for inclusion			→	→	→	→	→	→	→	→	
Patient enrollment			→	→	→	→	→	→	→	→	
Intervention											
Real-time ABCDEF electronic dashboard				→	→	→	→	→	→	+/-	
RN ABCDEF Implementation Facilitator				→	→	→	→	→	→	+/-	
Assessments											
Demographic data			→	→	→	→	→	→	→	→	
Laboratory data			→	→	→	→	→	→	→	→	
Vitals			→	→	→	→	→	→	→	→	
ICU and hospital medication data			→	→	→	→	→	→	→	→	
Primary Implementation Outcomes			→	→	→	→	→	→	→	→	
Primary Clinical Outcome			→	→	→	→	→	→	→	→	
Secondary Clinical Outcomes			→	→	→	→	→	→	→	→	
Work Intensity Data			→	→	→	→	→	→	→	→	
Intervention Acceptability, Barriers, and Facilitators										X	
Data Analysis											X

ACBDE assess, prevent, and manage pain; Both spontaneous awakening and breathing trials; Choice of analgesia/sedation; Delirium: assess, prevent, and manage; Early mobility/exercise; and Family engagement/empowerment; *ICU* intensive care unit, *RN* registered nurse

and all statistical analyses will occur. Access to study data after upload will be limited solely to the project statistician and project staff as authorized by the IRB. No extraction or transfer from the AWS repository other than as required by NIH following the publication of project reports will be allowed. The third study objective will use a secure web application to build and manage online surveys (REDCap). Focus group audio recordings will be stored in a Microsoft Office 365 application (including SharePoint, OneDrive for Business, Teams, or Streams).

Confidentiality {27}

Only masked data will be presented during the open sessions of the DSMB meetings. All data, whether in a report or discussed during a DSMB meeting, is confidential. Participant identities will be kept confidential unless safety concerns necessitate unmasking some or all data.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

N/A.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Descriptive statistics

In accordance with CONSORT extension guidelines for stepped-wedge cluster randomized trials, descriptive statistics will provide summaries at the cluster, period, and participant levels. Cluster characteristics will include the cluster number, the number of participants per cluster, the cluster's ICU type, the cluster's bed size, and key aspects of case mix. Period-level statistics will

consist of a per-period summary, including the number of clusters in the intervention versus the control at each step, the number of enrolled participants at each step, and participant characteristics and primary outcomes over time to assess for secular trends. Participant descriptive statistics will include overall baseline characteristics, as well as baseline characteristics by cluster, period, and intervention versus control within periods. Variables will consist of demographics (e.g., age, sex, race, Wisconsin neighborhood deprivation index [91], rural–urban commuting area codes [92]), comorbidities (e.g., Charlson comorbidity index [93]), and severity of illness metrics (e.g., hospital LOS before enrollment, Acute Physiology and Chronic Health Evaluation II score [94], Sequential Organ Failure Assessment Score [95, 96], readmission risk score [97]).

Objective 1 The analysis plan will be conducted on two levels: modified (mITT) and true intention to treat (ITT) [98, 99]. Since this study is focused on the adoption of the ABCDEF bundle on iMV patients by ICUs, patients who were placed on iMV prior to admission to the ICU or whose iMV straddles transition points in the study will be excluded from the primary analysis (mITT). The ITT secondary analysis will include those patients who were on iMV before ICU admission and those who straddle transition points. We anticipate the effect of Strategy A will initially be greater than that of Strategy B, with Strategy B showing a greater effect than Strategy A by the second time period following exposure. To account for the anticipated differing effect profiles, an exposure time indicator (ETI) model will be utilized [100]. The ETI model will be fit using a generalized linear mixed model with random effects for ICU and treatment effect and fixed effects for time and treatment effect. The model will have the following form:

$$g\left(\pi_{ijtk}|\gamma_i, \alpha_{j(i)}, u_{sk}\right) = \mu + \beta_t + \gamma_i + \alpha_{j(i)} + \left(u_{sk} + \partial(s_{jt})_k\right)X_{jt(k)}$$

where subscript i identifies the hospital, j the ICU, k the strategy, and t the calendar time. The term μ is the baseline log odds for the control condition, β_t is the underlying time trend, $\partial(s_{jt})_k$ is the kth treatment effect at exposure time s_{jt},$X_{jt(k)}$ is 1 if ICU j is on strategy k at time t and 0 otherwise, s_{jt} is exposure time of ICU j at time t, γ_i is the random effect of hospital, $\alpha_{j(i)}$ is an ICU specific random intercept and is assumed N(0, σ_α^2), u_{sk} is a random treatment effect assumed N(0, σ_k^2), and $\gamma_i, \alpha_j, u_t, and u_{sk} and e_{ijtk}$ are assumed to be mutually independent. The estimand of interest is the long-term treatment effect defined as the time-averaged treatment effect (TATE) between time 3 and 8 [100].

The analysis will be adjusted for patient-level covariates (not reflected in the model above for clarity) that were present before ICU admission: sex (sex at birth: male, female, ambiguous, other), age (age at ICU admission: equal to the time [in years and days] between the date of ICU admission and the patient's date of birth), race (American Indian or Alaska Natives, Asian, Black, Native Hawaiian or Other Pacific Islander, White, multiple races), insurance status (Medicare, Medicaid, dual eligible (Medicare and Medicaid), private, self-pay, other), rurality (4-tier classification scheme [urban, large rural, small rural, and isolated] based on the rural–urban commuting area codes [101]), Charlson comorbidity score [93], LOS in hospital prior to ICU admission, LOS in ICU prior to iMV, and duration of iMV prior to ICU admission. We are specifically interested in whether race (non-white vs. white) modifies the effect of the intervention on bundle performance. As such, we will specifically examine race-intervention interaction terms to understand the extent to which race may change the effect of specific interventions on the proportional performance of the ABCDEF bundle.

The primary comparison of interest is strategy A vs strategy B. There are two secondary comparisons of interest: strategy A vs control and strategy B vs control. The secondary comparisons will explore the effect of real-time A&F and RN implementation facilitation over standard practice, respectively. For each intervention, the estimand of interest is the long-term treatment effect defined as the TATE between time periods 3 and 8 [100]. This estimand is a weighted average of the individual $\partial(s_{jt})_k$ for each k. Type 1 error rate will be controlled at 0.05 by utilizing the Holm-Bonferroni adjustment for multiple comparisons.

Objective 2 Individual-level clinical outcomes will be analyzed utilizing the same modelling strategy outlined for Aim1, 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 Objective 1 analysis plan will be considered in all Objective 2 analyses. Biologically reasonable interactions (at the individual level) will be considered but only retained in models if the p-value is ≤ 0.10.

Objective 3a The time trend of work intensity, as measured by the NASA-TLX (range 0–100) [83], will be assessed using two methodologies: (1) tabulated simple descriptive statistics and a line plot of the mean NASA-TLX scores by exposure time and implementation strategy and (2) an exposure time indicator model similar to

that used in Objective 1 with the exception that the identity link will be utilized.

$$Y_{ijtk}|\gamma_i, \alpha_{j(i)}, u_{sk} = \mu + \beta_t + \gamma_i + \alpha_{j(i)} + \left(u_{sk} + \partial(s_{jt})_k\right)X_{jt(k)} + e_{ijtk}$$

where subscript i identifies the hospital, j the ICU, k the strategy, and t the calendar time. The term μ is the shared mean, β_t is the underlying time trend, $\partial(s_{jt})_k$ is the k^{th} treatment effect at exposure time s_{jt}, $X_{jt(k)}$ is 1 if ICU j is on strategy k at time t and 0 otherwise, s_{jt} is the exposure time of ICU j at time t, γ_i is the random effect of hospital, α_j is an ICU-specific random intercept and is assumed N(0, σ_α^2), u_{sk} is a random treatment effect assumed N(0, σ_k^2), e_{ijtk} is the random deviance, and $\gamma_i, \alpha_j, u_{sk}, and e_{ijt}$ are assumed to be mutually independent.

Anticipating an initial uptick, followed by a downward deceleration to stability in work intensity, the estimand of interest is the TATE between time periods 3 and 8. To be able to explore the work intensity perception across respondent characteristics, the analysis will be adjusted for respondent level (level 1) covariates: sex, age (categorized in decades), race (white vs non-white), strategy exposure time, and provider type. For clarity, the level 1 covariates are not reflected in the model above. We are specifically interested in whether race (non-white vs. white) modifies the effect on work intensity perception. As such, we will examine race-intervention interaction terms to understand the extent to which race may change the effect of strategy on perceived work intensity.

Objective 3b The acceptability of the two interventions will be compared in two ways: (1) tabulated five-number summary by implementation strategy and side-by-side boxplot of acceptability scores and (2) a linear mixed model with strategy as a fixed effect and random effects for hospital and ICU.

$$Y_{ijk}|\gamma_i, \alpha_{j(i)} = \mu + \beta_k X_{j(k)} + \gamma_i + \alpha_{j(i)} + e_{ijk}$$

Subscript i identifies the hospital, j the ICU, and k the strategy. The term μ is the shared mean, β_k is the effect of strategy k, $X_{j(k)}$ is 1 if ICU j is on strategy k and 0 otherwise, γ_i is the random effect of the hospital and is assumed N(0, σ_γ^2), $\alpha_{j(i)}$ is an ICU-specific random intercept and is assumed N(0, σ_α^2), e_{ij} is the residual assumed N(0,σ^2), and $\alpha_j, \gamma_i, and\ e_{ij}$ are assumed to be mutually independent. To explore the acceptability of the two strategies across respondent characteristics, the analysis will be adjusted for respondent level (level 1) covariates: sex, age (categorized in decades), race (white vs. non-white), strategy exposure time, and provider type.

Objective 3c The association of work intensity with adoption rate and acceptance will be quantified separately using Spearman's rank correlation. The ICU-level best linear unbiased prediction (BLUP) of work intensity for each calendar time will be averaged to arrive at an "overall" work-intensity (OWI) score for each ICU. Spearman's rank correlation will be computed between the individual OWI scores and each ICU's BLUP of acceptability. Spearman's rank correlation was chosen due to the small number of ICUs ($n=12$) and the fact that there are too few ICUs to support meaningful models.

Objective 3d For focus group interview analysis, following Lam et al.'s approach, we will conduct a template analysis of interview transcripts to identify themes describing experiences and perceptions of the proposed implementation strategies related to the consolidated framework for implementation research (CFIR) constructs [102]. Using the CFIR coding as a template, we will conduct hierarchical and structural coding to meet the proposed study's special needs. Multiple coders will review and discuss the CFIR coding definition and 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, the results of the quantitative and qualitative analysis will be synthesized to gain a deep understanding of stakeholders' perspectives on acceptability and provider work intensity.

Interim analyses {21b}

Pre-specified interim analyses will not be conducted to evaluate conditional power, futility, or efficacy, thus preserving the overall type I error probability regarding the interventions' efficacy.

Methods to handle protocol nonadherence and any statistical methods to handle

Missing data {20c and 31c}

ICUs are controlled environments where documentation of actions taken on a patient's behalf is 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 prevents the determination of whether a bundle element was performed (e.g., on iMV but no SBT is documented) will be treated as if that bundle element was not performed. If the data is not recoverable, analyses will be run using list-wise deletion

(reduced data set) and multiple imputations. 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 is any systematic characteristic that defines the missingness.

Survey data is collected in person by the site CRCs; therefore, we only anticipate missing survey observations when ICU staff refuse to respond to certain questions. Site CRCs will review responses as the surveys are collected; since an incomplete survey may be due to oversight by the respondent, the CRC will ask the respondent to complete the skipped question. If the staff member refuses to complete it, they will be asked why, and the reason will be annotated on the survey form. Missing data due to refusal to respond is not missing at random. Therefore, analyses will be conducted using complete data, followed by sensitivity analysis.

Plan to give access to the full protocol, participant-level data, and statistical code {31c}

Full protocol, anonymized participant-level data, and statistical code will be made available in a publicly accessible repository following the completion of data collection and publication of the primary outcomes paper.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The University of Nebraska Medical Center serves as the coordinating center for day-to-day trial support and oversight of intervention implementation, data management, and data analysis. A twice-monthly meeting is held, which includes all site PIs, project managers, data management, and statistical analysis personnel.

Composition of the data monitoring committee and its role and reporting structure {21a}

Data and Safety Monitoring Board (DSMB)

This clinical trial has a DSMB. The DSMB is independent and acts in an advisory capacity to the National Institute of Heart, Lung, and Blood Research (NHLBI) and the National Institute of Nursing Research (NINR) directors to monitor participant safety and data quality and evaluate the study's progress. The BEST-ICU Trial DSMB consists of the following five voting members with expertise in the following fields: critical care medicine, nursing, implementation science, clinical trial methodology, ethics, and biostatistics. All DSMB members are independent from the study. Four members will constitute a quorum. Each meeting will require the presence of the DSMB chair, DSMB biostatistician, and the unblinded study biostatistician. If a DSMB member cannot complete their duties, the principal investigators and the remaining DSMB members, in coordination with NHLBI/NINR, will identify a suitable replacement. Members were selected by the study team in collaboration with the NHLBI and NINR program officials. The NHLBI director approved the composition of the DSMB and its membership.

The NHLBI and NINR program officials or designees attend each meeting. Should participant safety questions or other unanticipated problems arise, the chair or the NHLBI may call an emergency meeting of the DSMB at any time. In the case of a serious adverse event that results in death, the principal investigators are required to inform the NHLBI and NINR within 48 h of notification.

Adverse event reporting and harms {22}

We define an AE as any untoward medical occurrence for a trial participant that is not tracked as a clinical outcome, regardless of whether the event is considered study-related or not. In the BEST ICU study, we will also track the following potential adverse events, which we believe will be rare but potential consequences of the real-time A&F dashboard and/or RN implementation facilitator:

- Data breach of confidential, patient-level protected health information
- A&F dashboard error resulting in a clinical action that was not indicated and resulted in patient harm
- RN implementation facilitator action that was not indicated and resulted in patient harm
- ICU providers' feelings of being unduly pressured or coerced by either implementation strategy (i.e., real-time A&F dashboard, RN implementation facilitator)

All identified AEs will be assessed as to whether they are (1) related to study participation, (2) serious, and/or (3) unexpected according to standard definitions.

Study personnel will communicate regularly with clinicians in participating ICUs to solicit information about any potential AEs. We will also create a study website that will allow clinicians to confidentially report any potential AEs. Finally, clinicians will also have access to site PI and study PI contact information via the study flyers should they wish to contact them directly to report an event.

In the rare case that it is believed that a study procedure leads to an identified adverse event of a *specific* patient-participant, we will upload such adverse events on a study-specific website directed to a case report form. Information to be collected includes event

description; time of onset; assessment of seriousness, severity, relationship to study procedures or interventions, and expectedness; medical care received; outcome of event; and time of resolution/stabilization of the event. In the case of an unexpected death believed to be related to implementation intervention study procedures (as a direct result of the real-time A&F dashboard or the actions of the RN facilitator) or a serious unexpected suspected adverse reaction (SUSAR), they will notify the project coordinator. The coordinator will request the related hospital documents, contact clinicians, and follow up with principal investigators. The DSMB safety officer will review such events further. Similarly, we will report such cases to the IRB, NHLBI/NINR, and OHRP in keeping with the NHLBI/NINR Adverse AE and UP reporting policies.

Clinical outcomes (not considered adverse events) monitored for safety reporting

In this pragmatic, cluster-randomized, stepped-wedge trial involving critically ill patients who are at high risk for death or other adverse outcomes due to their underlying critical illness, we will systematically track a variety of clinical outcomes, including duration of iMV and death, and include these outcomes as part of the safety and effectiveness analyses for this study.

This approach, considering death and duration of iMV as outcomes rather than AEs, is common in critical care trials because these outcomes/events occur commonly in the ICU, and this system mandates that data regarding death, iMV, and expected outcomes be tracked systematically for all patients and analyzed appropriately. Listed below are clinical events that will be tracked as clinical outcomes and will not, therefore, be reported as AEs during the study (unless believed to be study-related and/or more severe or prolonged than expected given the nature of the underlying illness). Definitions of each are available in Table 1.

- Hospital mortality
- Duration of iMV during the index ICU stay, stratified by survival status
- Clinically significant falls acquired during hospitalization
- New tachyarrhythmias in the I*CU* > 24 h after enrollment requiring treatment
- Cardiac arrest in the *ICU* > 24 h after enrollment
- Reintubation within 24 h of extubation

Frequency and plans for auditing trial conduct {23}

For the A&F arm, we will perform routine audits to ensure the dashboard operation and fidelity are met. Research team members will perform a monthly implementation checklist that includes direct dashboard observation to ensure that all patients and bundle components are displayed correctly.

The study team will review unit scheduling and staffing data for the RN facilitator arm to ensure the RN implementation facilitator role is assigned as intended. An electronic form will be sent to all RN implementation facilitators at 3 and 6 months post-implementation to query their tasks in the participating ICU. Furthermore, study personnel will monitor implementation fidelity (monthly) using a study-developed checklist to monitor the core features delivered by the RN implementation facilitator at each site. The clinical research coordinator will select a 4-h shift each month to complete the CRC fidelity monitoring tool for tracking implementation fidelity.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants and ethical committees) {25}

The PIs will review all potential protocol changes. They will also be reviewed with all relevant study staff, site PIs, and program officials from the NHLBI and NINR. Once reviewed, we will submit them to the IRB for final approval and review all approved changes at scheduled DSMB meetings. The study coordinator will track all amendment history and coordinate appropriate storage and dissemination of protocol updates.

Dissemination plans {31a}

Trial investigators will have full access to the final trial dataset. There are no contractual agreements that limit such access to investigators. Investigators plan on publishing results for all pre-specified primary and secondary outcomes in the peer-reviewed literature. Trial results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement [103, 104]. Publications will include the publication of the full study protocol and access to statistical code, upon request for review.

Discussion

Survivors of critical illness frequently experience profound physical, mental, and cognitive health impairments that are initiated and/or exacerbated by known racial and socioeconomic health disparities and outdated ICU iMV and symptom management practices. This morbidity is potentially preventable through the ABCDEF bundle, a multicomponent, evidence-based intervention to improve team-based care.

While consistently proven safe and effective, the national ABCDEF bundle performance remains unacceptably low

as clinicians struggle with multiple barriers to bundle delivery. The long-term objective of the proposed work is to develop pragmatic and sustainable strategies to increase the delivery of evidence-based practices that lead to improved care for critically ill adults across various healthcare systems, particularly those serving populations with known health disparities (safety net hospitals).

We will conduct a pragmatic, stepped-wedge, cluster-randomized hybrid type 3 effectiveness-implementation trial. After creating pairs of 12 ICUs from 3 hospitals ($N=8{,}100$ patients on iMV), we will randomly assign ICUs within each pair to receive one of two strategies grounded in behavioral economic theory and implementation science to increase ABCDEF bundle adoption. The strategies include real-time A&F (strategy A) or an RN implementation facilitator (strategy B). The evaluated strategies target various ICU team members and known behavioral determinants of bundle performance.

The trial objectives are to compare the effectiveness of real-time A&F and RN implementation facilitator on ABCDEF bundle adoption (primary implementation outcome) and curation of iMV (primary clinical outcome). In addition to secondary implementation and clinical outcomes, we will identify and describe key stakeholders' experiences with, and perspectives on, the acceptability and impact on workload of the implementation strategies.

We expect study results to impact the field by developing simple yet effective ways of accelerating the reliable uptake of a variety of evidence-based ICU interventions that will address known health disparities in the ICU and ultimately improve the care and outcomes of millions of critically ill adults annually.

Trial status

Enrollment to date

Trial recruitment began July 1, 2024. We anticipate that recruitment will be completed by December 31, 2026. The most recent updated version of the protocol is from August 23, 2024, version 2.2.

Abbreviations

BEST-ICU	Behavioral Economic and Staffing Strategies To Increase Adoption of the ABCDEF Bundle in the Intensive Care Unit
ABCDEF	Assess, prevent, and manage pain; Both spontaneous awakening and breathing trials; Choice of analgesia/sedation; Delirium: assess, prevent, and manage; Early mobility; and Family engagement
RN	Registered nurse
ICU	Intensive care unit
iMV	Invasive mechanical ventilation
ANRT	Advanced noninvasive respiratory therapy
LOS	Length of stay
SCCM	Society for Critical Care Medicine
PADIS	Pain, agitation/sedation, delirium, immobility, and sleep disruption
SAT	Spontaneous awakening trial
SBT	Spontaneous breathing trial
RCT	Randomized controlled trial
NMC	Nebraska Medical Center
UIHC	University of Iowa Hospitals and Clinics
OSU-WMC	Ohio State University Wexner Medical Center
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
OHRP	Office for Human Research Protections
RT	Respiratory therapist
EHR	Electronic health record
IRB	Institutional Review Board
PI	Principal investigator
A&F	Audit and feedback
DSMB	Data Safety Monitoring Board
AE	Adverse event
NIH	National Institutes of Health
PCORnet	Patient-Centered Outcomes Research Network
SDH	Social determinants of health
ITT	Intention to treat
TATE	Time-averaged treatment effect
CFIR	Consolidated Framework for Implementation Research
CRC	Clinical research coordinator
NHLBI	National Institute of the Heart, Lung, and Blood Institute
NINR	National Institute of Nursing Research
SUSAR	Serious unexpected suspected adverse reaction

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-09331-6.

Additional file 1: Figure 1: Patient Flyer. Figure 2: ICU Provider Flyer. Figure 3: Final Real-Time Audit and Feedback Dashboard Definitions Green/Yellow/Red by Bundle Element. Table 1: Patient Demographic and Clinical Data Collection Variables and Schedule. Table 2: CPT/ICD Codes in BEST ICU. Table 3: Oral Morphine Equivalents for Opioid Utilization20. Table 4: Sedative and Hypnotic Medications. Table 5: Antipsychotic Medications. Table 6: Medications Prescribed for Extrapyramidal Side Effects. Table 7: Antiarrhythmic Medications for the Treatment of New Arrhythmias.

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Authors' contributions {31b}

Designed the interventions, EV, JK, CW, RH, JC, CG, JB, BH, AB, KC, AW, JM, ME, AG, AK, JB, and MB. Obtained funding, EV and MB. Initiated the study design, EV, JK, CW, RH, JC, CG, JB, BH, AB, KC, AW, JM, ME, AG, AK, JB, and MB. Drafted the protocol, EV, JK, CW, RH, JC, CG, JB, BH, AB, KC, AW, JM, ME, AG, AK, JB, and MB. All authors contributed to the refinement of the protocol, and all authors read and approved the final manuscript.

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Data availability {29}
Study statisticians, Drs. Balas and Vasilevskis, will have final access to the trial dataset.

Declarations

Consent for publication {32}
Not applicable.

Competing interests {28}
The study leadership, in conjunction with the NHLBI and NINR, has established policies and procedures for all study group members to disclose all conflicts of interest. Participating sites have mechanisms in place for managing all reported dualities of interest. Dr. Balas is currently a paid consultant for the American Association of Critical Care Nurses' Healthy Work Environment Collaborative. She recently served as Co-Chair of the Society of Critical Care Medicine's PADIS guideline update and as a member of the American Psychiatric Association Delirium Guideline Writing Group. Dr. Hetland's current research efforts are supported by the Gordon and Betty Moore Foundation through Grant GBMF9048 and the National Institute of Health through award R41NR020458. She is also the CEO of FamilyRoom, LLC. Dr. Gerlach serves as a member of the Society of Critical Care Medicine Board/Council. Dr. Krupp's current research efforts are supported by the Agency for Healthcare Research and Quality under award number 5R21HS0299590-02. She recently served as a member of the Society of Critical Care Medicine's PADIS guideline update.

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