Published in final edited form as:

Crit Care Med. 2021 August 01; 49(8): 1254–1275. doi:10.1097/CCM.0000000000005131.

The Coming of Age of Implementation Science and Research in Critical Care Medicine

Juliana Barr, MD, FCCM[1,2], **Shirley S. Paulson, DNP, MPA, RN, NEA-BC**[3], **Biren Kamdar, MD, MBA, MHS**[4], **Jennifer N. Ervin, PhD**[5], **Meghan Lane-Fall, MD, MSHP, FCCM**[6,7], **Vincent Liu, MD, MS**[8,9,10,11], **Ruth Kleinpell, PhD, RN, FCCM**[12]

[1]Anesthesiology and Perioperative Care Service, VA Palo Alto Health Care System, Palo Alto, CA.

[2]Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA.

[3]Regional Adult Patient Care Services, Kaiser Permanente, Northern California, Oakland, CA.

[4]Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of California, San Diego School of Medicine, La Jolla, CA.

[5]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI.

[6]Department of Anesthesiology and Critical Care, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA.

[7]Penn Implementation Science Center at the Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, PA.

[8]Division of Research, Kaiser Permanente Northern California, Santa Clara, CA.

[9]Kaiser Permanente Medical Center, Santa Clara, CA.

[10]Stanford University, Stanford, CA.

[11]Hospital Advanced Analytics, Kaiser Permanente Northern California, Santa Clara, CA.

[12]Vanderbilt University School of Nursing, Nashville, TN.

Keywords

critical care; healthcare quality; implementation research; implementation science; patient safety

THE HISTORY OF IMPLEMENTATION SCIENCE IN CRITICAL CARE MEDICINE

The Institute of Medicine has long documented systemic deficiencies and significant gaps between the healthcare that critically ill patients should and actually receive. These gaps

For information regarding this article, barrj@stanford.edu.

exist across all healthcare settings, racial and ethnic groups, age groups, and geographic areas (1). Some of this variation in care delivery can be attributed to a lack of robust evidence to guide clinical practice (2). But even where high-quality evidence does exist and is widely disseminated through clinical practice guidelines with robust bundles of interventions and implementation strategies (i.e., Surviving Sepsis Campaign), many critically ill patients still do not receive the recommended care, contributing to their morbidity, mortality, and higher costs of care (3–5). To be both evidence-based and clinically useful, clinical practice guidelines must balance the strengths and limitations of all relevant research evidence with the practical realities of delivering care in complex and diverse clinical settings like ICUs (6). Many interventions proven to be effective in healthcare research often fail to translate to improved patient care and outcomes (7). In complex, dynamic organizations like healthcare systems, up to 70% of all change efforts fail to achieve full implementation of desired interventions (8, 9). This article explores the history of implementation science (IS), an emerging field that seeks to understand whether and how change is adopted in healthcare settings (10). Further, this review emphasizes the various reasons why critical care research often fails to translate into clinical practice and how IS can help to overcome these deficiencies to improve the quality, safety and value of care delivered to critically ill patients.

Historically, IS is said to have stemmed from a landmark report written in 1943 by Ryan and Gross on the diffusion of hybrid seed corn in two Iowa communities. According to Dearing and Kee (11), this seminal report, “set the paradigm for many hundreds of future diffusion studies by emphasizing individuals as the locus of decision, adoption as the key dependent variable, a centralized innovation change agency that employed change agents, and the importance of different communication channels for different purposes at different times in the individual innovation-decision process.” Rural sociologists began focusing on studying new research concepts in alignment with academia, and soon scholars in other fields began to synthesize approaches drawn together by both intellectual questions and funding opportunities for research.

IS expanded into healthcare in the 1960s and 1970s as scholars began questioning traditional assumptions as to how scientific advancements could influence real-world clinical practice (12). It was widely assumed at that time that if research was more readily available to healthcare providers, that implementation of best practices would automatically happen as practitioners applied this evidence to their everyday practice (13, 14). While clinical practice guidelines were created to make healthcare research more accessible and understandable, their application was challenging, requiring clinicians to read, interpret, accept, and consistently apply recommendations. This was not always possible, given the time constraints of most clinicians and the systemic cultural and structural barriers to change (13). IS has been used effectively to help narrow the gap between the discovery of new clinical knowledge and its application in public health, mental health, and other healthcare settings.

IS in critical care medicine has continued to evolve and expand over the past 50 years, influenced by the book of Rogers (15) “Diffusion of Innovations” (described later in more detail), by the studies of Weiss and Bucuvalas (16) policy decision-making and

the use of scientific inquiry to impact social change through policy action, and by the development of multicenter and international registries for conducting clinical trials and benchmarking clinical performance. The emergence of professional organizations such as the Society of Critical Care Medicine (SCCM) in 1970 (17) also helped to highlight the importance of setting professional standards and promoting excellence and consistency in the practice of critical care medicine. Traditional top-down approaches to implementation that rely heavily on high-level administrative oversight, clinical practice guideline committees, and conference speakers as subject matter experts (SMEs) are being supplanted with multifaceted, multidisciplinary approaches involving providers who are close to or directly at the point of care, often employing new implementation technologies (i.e., ICU telemedicine) (18).

Over the past 10–15 years, the business model of U.S. healthcare systems to maximize revenue has been steadily shifting away from reducing costs to increasing the "value" of healthcare (19). Laws in the United States, such as the Affordable Care Act, have helped to accelerate this change through the creation of incentive mechanisms, such as Accountable Care Organizations (ACOs) and the Hospital Value-Based Purchasing Program (20). ACOs align healthcare providers, often across hospital systems, to deliver coordinated, high-quality care to their Medicare patients (21). The overarching goal of ACOs is to effectively coordinate care to ensure that patients receive the right care in a timely fashion, while avoiding costly medical errors and redundancy of services. When an ACO succeeds in both delivering high-quality care and spending healthcare dollars more efficiently, the ACO shares in the savings, it achieves for the Medicare program. The Hospital Value-based Purchasing Program rewards acute care hospitals with incentive payments for the quality of care and the experience they provide to hospitalized patients (22). The Value-based Purchasing Program specifically incentivizes hospitals to: eliminate or reduce adverse events; improve adoption of evidence-based practices; improve the patient experience; and increase their transparency of care quality to consumers, clinicians, and other stakeholders. Increasing demand for improving the quality and value of healthcare delivery has also incentivized extramural funding organizations such as the National Institute for Health to invest more than 32 billion dollars annually to support the development of IS and implementation research efforts (23).

IMPLEMENTATION SCIENCE DEFINED

IS includes both implementation research (IR) and practice, with IR forming part of the continuum of translational research. Translational research integrates findings from basic science, clinical, and population health-based research, testing novel therapeutic strategies and accelerating these therapeutic interventions into clinical practice with the goal of improving patient outcomes (24–26). IR is a form of late-stage translational research, which yields generalizable knowledge regarding evidence-based interventions. These interventions help to disseminate and implement basic science and clinical research discoveries to improve population health (Fig. 1) (23, 27).

IS is broader than implementation itself; implementation practice uses systematic methods to adopt best practices, whereas IS seeks to understand how and why the adoption of

best practices either occurs or fails (18). IS is a branch of health services research that uses principles from organizational psychology, public health, operations management, epidemiology, and behavioral economics to evaluate implementation failures and to use this knowledge to develop and test strategies to overcome barriers and to close the evidence-practice gap (5). IS aims to strengthen the implementation of best practices and the de-implementation of ineffective practices and to ensure the uptake and sustainability of new and existing knowledge and experience. Implementation practice tends to use extant knowledge and tools to address implementation challenges, while IR is often focused on advancing the field of IS itself through the development of theory, measures, and innovative study designs.

CONCEPTUAL FRAMEWORKS FOR IMPLEMENTATION RESEARCH

Rogers, Greenhalgh, and Damschroder are among the many researchers who have proposed conceptual frameworks that provide a systematic way to develop, manage, and evaluate interventions to move new ideas into clinical practice (28). Conceptual frameworks provide a common vocabulary and classification scheme to help IRs and practitioners identify barriers to the adoption of evidence-based practices (29). Conceptual frameworks help to describe the implementation process, explain those factors that influence implementation outcomes, and evaluate the implementation itself (28). These frameworks are also critical for developing successful IR grant proposals (30). Although there is no single, reliable way to modify human behavior, IS and the application of conceptual frameworks have been used successfully to modify discrete aspects of medical practice (2). Understanding which implementation methods most effectively translate evidence-based therapies into clinical practice will help researchers design targeted implementation strategies for successful assimilation of best practices in critical care.

Greenhalgh et al (14) applied Rogers Diffusion of Innovation Theory to a systematic review of nearly 500 published sources across 13 fields of research, describing evidence-based strategies to successfully spread and sustain innovations in healthcare delivery and organization (31). They distinguished between strategies related to the “diffusion” (i.e., passive spread), “dissemination” (i.e., active and planned efforts to persuade target groups to adopt and innovation), “implementation” (i.e., active and planned efforts to mainstream an innovation within an organization), and “sustainability” (i.e., making an innovation routine until it reaches obsolescence) of innovations. They identified 11 key attributes of successful innovations that allow change to be more easily adopted, including “relative advantage, compatibility, complexity, trialability, observability, reinvention, fuzzy boundaries, risk, task issues, knowledge, and augmentation/support” (Table 1). The authors note that these innovation attributes are neither stable features nor sure determinants of their adoption or assimilation. Rather, it is the interaction between the innovation, the intended adopter(s), and the context that determines the innovation adoption rate. They recommend that IR questions should be framed to highlight processes rather than outcomes. For example, instead of asking, “Does program X work?”, one should frame the question, “What features account for the success of program X in this context, and the failure of a comparable program in a different context?”

Damschroder's Consolidated Framework for Implementation Research (CFIR) incorporated the work by Greenhalgh et al (14) and identified five major domains of variables that interact to influence the adoption of an innovation: 1) the characteristics of the innovation (i.e., strength of evidence, relative advantage, compatibility, etc.); 2) the inner setting (i.e., the structural and cultural characteristics of the organization); 3) the outer setting (i.e., regulatory policies and payment models); 4) the characteristics of the individuals involved (i.e., knowledge, beliefs, receptiveness to change); and 5) the implementation processes used (e.g., bottom-up vs top-down decision making) (Fig. 2) (7). The CFIR has been widely used to help identify facilitators and barriers to implementation of evidence-based practices (32, 33). While most attention within the CFIR is focused on how to more quickly adopt and spread innovations that will benefit patients, this framework can also be used to help understand how organizations can eliminate treatment, practices, and policies that no longer benefit patients, referred to as "de-implementation" or "exnovation (34)."

DELAYS IN WIDESPREAD ADOPTION OF EVIDENCE-BASED RESEARCH

It is often stated that it takes an average of 17 years for evidence-based research to be incorporated into mainstream clinical practice (35–37). Extensive delays in adopting evidence-based best practices result in a significant waste of scarce resources and a loss of potential benefits to patients. In 2011, Morris et al (38) studied the time lags in translational research and described this lack of, "a timely realization of the benefits of expensive medical research" as an area of, "international concern." They described 23 specific examples of significant delays in the translation of research into clinical practice. In the United States alone, these included significant delays in the adoption of treatment strategies for acute myocardial infarctions (i.e., a time lag of 6–13 yr), the top 10 clinical advances in cardiovascular and pulmonary medicine and surgery (i.e., a time lag 30.6 yr), and the management of AIDS (i.e., a time lag 2.6–3.8 yr).

There are several potential challenges in expediting the widespread adoption of evidence-based medicine (6, 13, 38). The initial path of biomedical research typically requires rigorous evaluation and funding to conduct high-quality research that yields strong evidence. The evidence then needs to be synthesized, ideally with a clinical practice guideline developed from the evidence. The evidence-based practice must then be applied to appropriate clinical settings in a way that balances those CFIR attributes of the conceptual framework, which support the innovation. These steps must be negotiated across various stakeholder groups to form a valid connection between evidence and practice. Clinician motivation to change what they are currently doing, the size and complexity of the research, difficulties in applying the evidence in practice, and organizational barriers may all contribute to delays in the translation of evidence into clinical practice. IS and IR can help to identify and overcome these barriers in the ICU setting, to accelerate the adoption of evidence-based medicine, and to improve ICU patient care and outcomes using a structured, team-based approach (Fig. 3).

Below, several critical care practice guidelines and recommendations are presented, with an explanation of how IS might be applied to enhance uptake and use. It should be noted, however, that the strength of the evidence underpinning these guidelines and

recommendations is mixed. Some of the variation in uptake and use of these guidelines is almost certainly explained by three factors: variability in the quality of supporting evidence; the practice of bundling interventions that have been individually proven to be effective but have not yet been tested as a bundle of interventions; and a history of high-profile reversals in critical care evidence. These reasons for skepticism notwithstanding, it is worthwhile to identify and address challenges to implementation once a decision has been made to adopt specific clinical practices.

TRANSLATING RESEARCH INTO CRITICAL CARE PRACTICE

Table 2 summarizes the major critical care practice recommendations developed over the past 25 years that are relatively low-cost and supported by high-quality evidence demonstrating improved patient outcomes. Despite their benefits, most of these best practices have not been fully integrated into the routine practice of critical care medicine. We explore three of these interventions in more detail (i.e., lung protective strategies in patients receiving invasive mechanical ventilation, the central line-associated bloodstream infection bundle, and the ICU Liberation Bundle), to better understand the barriers to adopting these best practices in the context of IS and CFIR domains.

Lung Protective Strategies in Mechanically Ventilated Patients

Acute respiratory distress syndrome (ARDS) is a severe form of hypoxic respiratory failure associated with various etiologies, most commonly sepsis, pneumonia, aspiration, trauma, and multiple blood transfusions (74–78). ARDS results from acute pulmonary inflammation, diffuse alveolar damage with increased capillary permeability, and the development of nonhydrostatic pulmonary edema, with patients often requiring intubation and invasive mechanical ventilation (75, 76, 79, 80). Worldwide, the estimated prevalence of ARDS ranges from 7.2 to 34 cases per 100,000 person-years and accounts for 10% of all ICU admissions and 23% of mechanically ventilated ICU patients (81–84). Historically the ARDS case fatality rate was around 60%, but over the past 20 years, mortality from ARDS has decreased by more than 50% (85–87). Improved survival from ARDS is attributable to general improvements in critical care management, along with specific improvements in ARDS management, particularly the use of “lung protective strategies” in invasive mechanical ventilation to prevent barotrauma in patients. Lung protective ventilation (LPV) is the use of low tidal volumes (i.e., 4–8 mL/kg based on ideal body weight), while maintaining a plateau pressure of less than 30 cm H_2O using lower inspiratory pressures during invasive mechanical ventilation (88, 89).

Several systematic reviews and meta-analyses confirm that patients diagnosed with ARDS who receive LPV experience lower morbidity and mortality, fewer ventilator days, and shorter ICU and hospital lengths of stay (90–95). LPV in ARDS is widely endorsed internationally by pulmonary and critical care societies (96), yet LPV remains very underutilized, delivered to only 1/3 of patients with ARDS receiving invasive mechanical ventilation (84). Several barriers to LPV delivery in ARDS patients have been proposed, including: 1) guideline factors (e.g., which patients should receive LPV, when should LPV be initiated in patients, variable performance metrics) (i.e., “CFIR intervention

characteristics domain"); 2) ICU factors (e.g., a lack of formal LPV protocols, a lack of role clarity for ventilator management, poor team communication) (i.e., "CFIR inner setting domain"); and 3) clinician factors (e.g., failure to diagnose ARDS in patients, knowledge deficits, negative attitudes toward LPV and evidence-based practices in general, perceived contraindications, safety concerns) (i.e., "CFIR individual characteristics domain") (97–102).

Multiple strategies have been shown to significantly improve LPV compliance and adherence in patients with ARDS. These include: 1) having a written LPV protocol; 2) provider education; 3) daily multidisciplinary rounds involving checklists and goal setting; 4) establishing low tidal volumes as the default ventilator setting for all mechanically ventilated patients; 5) ARDS Clinical Decision Support for providers included in the Electronic Health Record (EHR); and 6) provider audit and feedback (103). With the exception of daily team-based ICU rounding using checklists and goals sheets, none of these interventions when implemented alone have achieved compliance with LPV in the "majority" of patients with ARDS (104).

Central Line-Associated Blood Stream Infections

Central line-associated bloodstream infections (CLABSIs) are common yet preventable healthcare-associated complications, with the majority occurring in critically ill patients. CLABSIs comprise nearly three-quarters of all nosocomial bloodstream infections, with 80,000 CLABSIs occurring in ICU patients annually in the U.S. CLABSIs are associated with significantly longer ICU lengths of stay and lead to 30,000 deaths annually in these patients and up to $2.3 billion in additional healthcare costs (105).

Evidence-based interventions to prevent CLABSIs have resulted in significant reductions in ICU CLABSI rates over the past decade. In 2006, Pronovost et al (58) demonstrated that a CLABSI prevention checklist, implemented as part of a statewide ICU quality improvement (QI) project in Michigan, significantly reduced statewide CLABSI rates in ICU patients. The checklist included five evidence-based interventions recommended by the Centers for Disease Control and Prevention to help prevent CLABSIs including: 1) provider hand washing prior to the procedure; 2) full barrier precautions during catheter insertion; 3) skin preparation with chlorhexidine; 4) judicious selection of a catheter insertion site (i.e., avoiding the femoral vein); and 5) removal of unnecessary catheters in a timely fashion (106). Bundle compliance was optimized with routine checklist use, central line placement supply carts, daily discussions regarding catheter removal, frequent performance reports, and direct observation of catheter placement by bedside staff who were empowered to stop providers if checklist items were not followed. Across the 103 ICUs participating in the intervention, median CLABSI rates declined from 2.7 per 1,000 catheter days to zero CLABSIs at 3 months.

Following this groundbreaking study, the Infectious Disease Society of America published CLABSI prevention guidelines recommending that this CLABSI prevention checklist be used in all acute care hospitals (107, 108). Importantly, these guidelines also reinforced core implementation principles, including engagement of multidisciplinary teams to foster a culture of patient safety, innovative educational programs aimed at changing

provider behavior, use of established intervention methods, and ongoing process evaluation and improvement (i.e., “CFIR domains of inner setting, individual characteristics, and implementation processes”) (109). Further motivating practice change, in 2008, the Centers for Medicare and Medicaid added vascular catheter-associated infections to the list of hospital-acquired complications that were no longer eligible for reimbursement (i.e., “CFIR outer setting domain”) (110).

Widespread implementation of CLABSI prevention bundles using effective implementation strategies has significantly reduced the overall prevalence of CLABSIs in the United States as well as in other countries. A recent meta-analysis of 79 studies evaluating the impacts of implementing CLABSI prevention bundles in adult, pediatric, and neonatal ICUs demonstrated a 60% reduction in CLABSI rates (i.e., from 6.4 [interquartile range (IQR), 3.8–10.9] to 2.5 [IQR, 1.4–4.8] CLABSIs per 1,000 catheter days and incidence rate ratio [IRR], 0.44; 95% CI, 0.39–0.50; $p < 0.0001$; $I^2 = 89\%$) (111). Bundle elements having the greatest impact on CLABSI risk reduction were: hand hygiene prior to catheter insertion ($p = 0.003$) and maintenance ($p = 0.022$); use of a central venous catheter line cart containing all necessary supplies ($p < 0.0001$); avoiding the femoral vein as an insertion site ($p = 0.03$); and minimizing central line access ($p = 0.019$). Implementation strategies included: staff education, academic detailing, use of local champions or opinion leaders, checklist use, protocols, audit and feedback, reminders, leadership engagement, and organizational restructuring. Staff education, audit and feedback, organizational change, checklist use, and protocols were used in over 50% of these studies. Implementation strategies with the greatest impact on CLABSI risk reduction included the strong support and leadership of opinion leaders ($p = 0.041$), combined with strict protocol or checklist compliance, and when nurses were empowered to stop the procedure if a physician breached the central line insertion protocol (112).

It is important to note that these significant reductions in CLABSI rates occurred despite suboptimal compliance by providers with bundle protocols. In a separate large cross-sectional study comparing CLABSI rates with protocol compliance in nearly 1,000 U.S. ICUs that are part of the National Healthcare Safety Network, there was a strong dose-response effect seen between bundle compliance and CLABSI rate reductions (113). Bundle elements included: 1) hand hygiene prior to insertion; 2) maximal barrier precautions; 3) chlorhexidine skin prep; 4) avoidance of femoral vein as an insertion site; and 5) daily review of central line necessity. Although 98% of ICUs had CLABSI bundle policies in place, only 69% reported “excellent” compliance (i.e., 95% bundle compliance) with at least one bundle element, while 31% of ICUs failed to achieve 95% compliance with at any of the bundle elements. Only 20% of ICUs reported excellent compliance with all bundle elements, while 49% percent reported compliance with all five bundle elements at least 75% of the time. Simply having a written policy for a CLABSI prevention bundle was “not” associated with lower CLABSI rates. But the higher the bundle element compliance rates, the greater the observed reductions in CLABSI rates. Excellent compliance with all five bundle elements was associated with a 33% lower frequency of CLABSIs compared with excellent compliance with no bundle elements (IRR, 0.67; 95% CI, 0.59–0.77; $p < 0.001$).

Together, these studies suggest that greater widespread adoption of the CLABSI bundle will further decrease CLABSI rates in ICU patients, while also improving outcomes and reducing healthcare costs. But it remains to be seen whether healthcare providers achieving perfect compliance with the CLABSI bundle can eventually make CLABSIs a "never event (114, 115)." The use of IS and IR to improve adherence to the CLABSI bundle, along with the use of newer technologies to improve the safety of catheter placement and maintenance (e.g., ultrasound-guided placement, use of antibiotic-impregnated catheters, chlorhexidineimpregnated dressings, needleless securement devices and disinfecting caps) may further enhance CLABSI prevention efforts (116).

The ICU Liberation Bundle

Pain, agitation, and delirium (PAD) occur frequently in critically ill patients, and managing these symptoms can be difficult, leading to poorer outcomes and higher costs of care for patients (117). The ICU Liberation Bundle (aka, the Assess, prevent, and manage pain; Both spontaneous awakening and breathing trials; Choice of Sedation Strategies; Delirium assess, prevent, and manage; Early Mobility and Exercise; Family engagement and empowerment [ABCDEF] Bundle) (Fig. 4) was developed to help implement the SCCM's Pain, Agitation, Delirium, Immobility, and Sleep Clinical Practice Guidelines (118). This Bundle focuses on optimizing pain management, avoiding deep sedation, reducing the risk of delirium, shortening the duration of mechanical ventilation, reducing the risk of ICU-acquired weakness and sleep disruption in patients, and engaging ICU patients and families in care processes (72,119–121). Bundling pain, sedation, and delirium management together with ventilator weaning and early mobility efforts helps to standardize ICU care processes, reduce inter-provider practice variation, improve ICU team communication, and ensure that all ICU patients receive the Bundle every day. Compared with delivery of these interventions independently, bundling these practices together can translate to greater synergistic improvements in both short- and long-term patient outcomes and reductions in healthcare costs (72,119–122).

The ICU Liberation Bundle is supported by strong, high-quality evidence (i.e., "CFIR intervention characteristics domain") (118, 123). But translating this evidence into clinical practice can be challenging. Even in ICUs participating in large-scale structured QI efforts designed to promote Bundle adoption, implementation and performance of the Bundle elements vary significantly, and overall Bundle adoption across ICUs remains low (72, 124–126). Many ICU physicians and nurses are reluctant to maintain patients at a light level of sedation, to use respiratory therapist nurse driven ventilator weaning protocols, to mobilize ventilated ICU patients out of bed, or to engage patients and families in decision-making and care processes (i.e., "CFIR individual characteristics domain") (125, 127–133). Additional barriers to Bundle adoption include ICU staff knowledge deficits and safety concerns (i.e., "CFIR individual characteristics domain"), staffing shortages, a lack of leadership support for Bundle implementation and sustainability (i.e., "CFIR inner setting domain"), and a lack of institutional commitment to patient safety and QI efforts (i.e., "CFIR implementation processes domain") (124, 125, 130, 131, 134–136). Many ICU providers also lack effective teamwork and collaboration skills to effectively execute the Bundle (i.e., "CFIR inner setting and individual characteristics domains") (128, 134, 137). As a result, ICU patients are

often deeply sedated and mechanically ventilated for longer than necessary, placing them at greater risk of developing ICU delirium, muscle weakness, hospital-acquired infections, long-term physical and cognitive dysfunction (i.e., Post-Intensive Care Syndrome), and other preventable complications.

The ICU Liberation Bundle has the potential to significantly transform patient care and outcomes. ICU patients who receive the Bundle are typically more awake, alert, and more often pain-free (72). As a result, patients can interact more readily with their families and clinicians and are more able to actively participate in their care (e.g., ventilator weaning, mobility efforts) and decision-making. These patients recover faster, are ready to be transferred out of the ICU and discharged sooner, and are more likely to be discharged to home after their ICU stay. But successful execution of the Bundle requires: effective team communication, collaboration, and care coordination among providers (138–141); partnering with ICU patients and families to prioritize patient care goals (123, 142, 143); the use of real-time data to measure Bundle performance and outcomes; and strong leadership support for Bundle implementation and sustainability efforts (144–146). This often requires a transformational change in the way clinicians deliver care to patients. The use of evidence-based implementation strategies can significantly improve Bundle compliance and performance by improving teamwork and communication around the Bundle. We will use the SCCM's ICU Liberation Collaborative as one of two case studies demonstrating how IS and IR can be used on a large scale to help translate evidence into clinical practice.

CRITICAL CARE IS/IR CASE STUDIES

The ICU Liberation Collaborative

The ICU Liberation Collaborative was a 2-year, multicenter Bundle QI initiative including over 15,000 mechanically ventilated and nonmechanically ventilated adult ICU patients admitted to 69 community, government or academic hospitals across the United States. The Collaborative was sponsored by the SCCM with support from the Gordon and Betty Moore Foundation (147, 148). The purpose of the Collaborative was to equip ICUs with the skills and knowledge necessary to implement the ICU Liberation (ABCDEF) Bundle and to improve Bundle-related teamwork and collaboration (144).

The Collaborative was led by SMEs with expertise in the PAD Guidelines, implementation and dissemination research, and large-scale QI efforts. CFIR constructs and domains were used to develop evidence-based implementation strategies, Bundle process and outcome metrics, and to identify potential barriers and facilitators of Bundle implementation. Collaborative sites were recruited through social media and at national critical care meetings from three geographic regions in the United States (i.e., West Coast, Midwest, and East Coast). Each site had an interprofessional implementation team including physicians, nurses, respiratory therapists, physical or occupational therapists, and pharmacists. Teams attended four in-person meetings with faculty and participated in monthly co-learning calls and training webinars, database training sessions, an e-Community listserv, and SME site visits. Curriculum included the evidence behind each bundle element, as well as team-based implementation strategies for improving Bundle compliance and sustainability. Teams were also encouraged to share best practices with one another. Team members

collected and entered all patient-level data in the Collaborative's Research Electronic Data Capture (REDCap) database and completed pre- and post-implementation questionnaires that assessed teamwork and collaboration, work environment, and overall ICU care (149). All sites provided a letter of commitment from their ICU Medical Director and a senior Hospital Administrator verifying that their hospital was willing to provide the necessary time and resources for teams to be successful.

Results from the ICU Liberation Collaborative demonstrated that as Bundle compliance across sites increased, the use of mechanical ventilation, and the prevalence of coma, delirium, and restraint use in patients significantly decreased, while ICU and hospital lengths of stay, ICU readmission rates, hospital mortality, and the proportion of ICU survivors discharged to a skilled nursing facility also significantly decreased (72). Importantly, there was a consistent dose-response relationship observed between higher proportional bundle performance resulting in even greater improvements in these outcomes. Hsieh et al (121) have also demonstrated that even partial Bundle implementation is associated with significant reductions in ICU and hospital costs.

Common barriers to Bundle Implementation during the Collaborative included: 1) challenges with developing and operationalizing clinical protocols for pain, sedation, and delirium management; 2) nurse, respiratory therapist, and physician coordination of spontaneous awakening and breathing trials; 3) application of delirium assessment tools in neurologically impaired patients; 4) safely getting critically ill patients out of bed; 5) a lack of physical therapy staff; 6) challenges with directly engaging patients and families; 7) insufficient support by hospital administration; and 8) a lack of information technology resources to acquire and analyze Bundle metrics within the EHR (131, 150). These barriers highlight several attributes of the Bundle as an innovation (Table 1) (i.e., Bundle complexity, relative advantage, trialability, reinvention, observability of benefits, and relative risk; adopters' knowledge of the Bundle and its compatibility with their beliefs, and task issues; and augmentation and support), which map directly onto the five CFIR domains (Fig. 2).

The use of evidence-based implementation strategies during the Collaborative that facilitated Bundle compliance and performance included: 1) innovations to incorporate the Bundle into the daily ICU workflow (i.e., daily interprofessional team rounds at the bedside with facilitated team discussions of the Bundle and care plan [144, 151]; use of Bundle checklists and goal sheets [130]; EHR documentation of Bundle elements [145, 152]); 2) engagement of patients and families in team discussions about the Bundle and goals of care (123, 142, 153); 3) measurement of Bundle compliance and performance that was patient, provider, and unit specific through analysis of aggregated EHR Bundle data (154); and 4) strong leadership engagement and support of Bundle implementation efforts (124, 130).

Kaiser Permanente Northern California

Critically ill patients are at substantial risk of experiencing both short- and long-term morbidity and mortality (155–159). For over 10 years, Kaiser Permanente of Northern California (KPNC) has invested in IS to mitigate adverse outcomes and restore patient health following intensive care and hospitalization (160). As a highly integrated healthcare

delivery system serving 4.4 million members across 21 hospitals, the use of IS has provided KPNC with scalable, reliable, and sustainable approaches to deliver high-quality care across the healthcare system (161–165). These approaches have been applied across a diverse range of inpatient programs, each offering an incremental contribution to improving ICU outcomes in alignment with patients' goals of care. It's important to note that unlike most other healthcare systems in the United States, physicians in the Kaiser Permanente (KP) system are full-time employees, whose compliance with defined bundles and guidelines are monitored through the EHR, and whose performance is judged at least in part by that compliance, which may provide significant financial incentives to KP physicians.

In 2008, KPNC leaders conducted a mortality diagnostic survey to identify gaps in care contributing to adverse outcomes across the health system's 21 hospitals (166). This systematic approach revealed sepsis as the single largest contributor to inpatient death, while also highlighting opportunities to improve care (167). Numerous barriers were identified that impeded the reliable delivery of timely care to septic patients at the provider, facility, and health system levels (160). The resulting KPNC Sepsis Program used key IS tenets to devise innovative solutions to overcome barriers, resulting in substantial improvements in sepsis-related process and outcome metrics (166). This approach also enabled KPNC to identify new sepsis-related opportunities, particularly in populations for whom little prior data existed (e.g., septic patients with intermediate lactate levels) (168–174). These advances highlighted the role of IS in promoting a continuously learning healthcare system to systematically improve care for all patients with sepsis across the healthcare system (165).

KPNC's use of IS to systematically improve sepsis care fostered new programs designed to bring evidence-based care to critically ill patients. Using a similar approach, KPNC focused on *Clostridium difficile* and hospital-acquired infection prevention (160, 175, 176), mechanical ventilation liberation (177), delirium prevention (178, 179), patient mobility (177, 180), enhanced recovery after surgery (180–182), regional tele-stroke management (183), conservative blood transfusion management (184–186), opiate exposure reduction (182, 187), palliative care management (188), readmission prevention (189, 190), and prevention of inpatient deterioration through early warning systems (191–193). Each of these efforts leveraged: 1) QI initiatives and iterative improvement cycles; 2) granular and high-quality data and metrics available through the EHR; 3) change management approaches bringing together diverse content experts, clinicians, and stakeholders; 4) consistent aims and messaging via a governance structure aligning both regional and local leaders; and 5) the delivery of patient-centered care. KPNC also continues to focus on preventive care by identifying potent opportunities to reduce hospitalization rates and ICU admissions in order to mitigate the unintended and deleterious consequences of inpatient care. For more than a decade, KPNC has successfully used IS and IR to develop reliable and sustainable approaches to improve the value, quality, and safety of ICU care across their healthcare system.

FACILITATING THE UPTAKE OF EVIDENCE-BASED PRACTICE IN CRITICAL CARE

At its core, IS is the science of behavioral change in healthcare delivery. For this reason, behavior change theories and principles are often invoked when designing implementation strategies to facilitate the uptake of evidence-based practices. Behavior change theories relevant to IS and practice include those focused on change at the “individual” (e.g., the Theory of Planned Behavior [194] and the Theoretical Domains Framework [195]), “team” (e.g., the Team Performance Framework [196]), and “institutional” (e.g., Organizational Theory of Innovation Implementation [197]) levels. The socio-ecologic framework (198) illustrates behavior change strata that can be used to categorize the many theories, frameworks, and models that have been applied to IS. More comprehensive overviews of implementation frameworks are provided by Tabak et al (199) and Nilsen (28).

The behavior change sought by IRs and practitioners is created through implementation strategies, which are the actions through which behavior change is achieved. Proctor et al (200) said that implementation strategies, “comprise deliberate and purposeful efforts to improve the uptake and sustainability of treatment interventions.” More than 70 discrete implementation strategies were identified in a recent initiative called the Expert Recommendations for Implementing Change (ERIC) (201), and include recruiting, designating and training leaders for the change effort, training and educating stakeholders, staging implementation scale-up with small pilots or demonstration projects, tailoring implementation strategies to address potential barriers, and using a train-the-trainer strategy (201, 202). Indeed, no implementation effort would be expected to use all or even most implementation strategies identified by the ERIC initiative. Rather, the ERIC strategies represent a “menu” of strategies that “could” be applied to a given implementation effort (201).

How should implementation strategies be selected? The field of IS has since moved away from the arbitrary selection of strategies based on what researcher Martin Eccles calls the ISLAGIATT principle (“it seemed like a good idea at the time”) (203). Increasingly, researchers use theory and contextual inquiry to select strategies in a process known as “implementation mapping (204).” With this method, determinants of implementation (i.e., barriers and facilitators) are “mapped” onto specific strategies to address implementation barriers. For example, if a needs assessment identifies a knowledge deficit as an important factor in the underuse of an evidence-based practice, education and training would be reasonable strategies in this instance. The opposite is also true; if knowledge is not a problem, education and training are unlikely to facilitate implementation. In addition to mapping, Powell et al (205) offer three other approaches for selecting and tailoring implementation strategies: concept mapping, group model building, and conjoint analysis.

Appropriate implementation strategies will differ depending on the setting and focus of a given effort. Although implementation barriers may transcend all five CFIR domains, most fall within the individual and inner settings domains. These domains include logistical barriers to implementing evidence-based practice at the institutional and clinician levels (2). While institutional support for implementation is essential, at the clinician level, time,

access to resources, and their eagerness to apply research in clinical practice pose significant challenges (2). The theme of early and continuous stakeholder engagement has also been identified as especially important to the success of IR in targeting clinical improvement initiatives (10).

Specific strategies to be considered in ICU implementation efforts include those that promote team-based and patient-centered care. For example, targeted team training can help foster leader inclusiveness and psychological safety among team members, which facilitates information sharing, problem solving, and decision making within the team (206–208). As promotion of team-based behaviors in the ICU tends to require more complex and bundled approaches, protocols and educational materials should emphasize role clarity of team members and the understanding and appreciation of each individual's knowledge, skills, abilities, and responsibilities, an approach associated with enhanced care coordination, collaboration, and team performance (138). Additionally, education, training, and audit and feedback strategies should be used to promote effective team communication and performance, including interdisciplinary bedside rounds, checklists, and EHR use (134, 151). These strategies help teams to establish and reinforce shared goals, engage in open exchanges of information, and to solve problems collectively. As described above, the use of theoretical models such as the team performance framework may help identify and address the complexities of ICU team dynamics that can influence implementation efforts (196). In critical care, changing ICU culture is often cited as a key component to implementing best practices. Challenges in recruiting ICU staff to become team-based champions and clinician resistance, including perceptions that change will increase their workload and challenge their practice autonomy, are key factors to address when planning and implementing new clinical initiatives (209–211). Ensuring that ICU staff and leadership have a clear understanding of the project's goals is also essential.

A specific example shows how to link implementation determinants to effective strategies. A recent national collaborative initiative involving 63 ICUs implemented a patient- and family-centered care initiative over a 10-month period. Major barriers included a lack of buy-in, an inability to promote change in the clinical setting, an implementation-related increase in workload, and insufficient funding to support these initiatives (212). Strategies cited to address implementation barriers included gaining stakeholder buy-in, enlisting unit-based champions, communicating implementation status, and sharing examples of progress including comments from clinicians, family members, and patients regarding the benefits of the practice change. As there is no "done" to the clinical improvement process in critical care, successful efforts require ongoing persistence in messaging, education, measurement of performance and outcomes, and iterative reinforcement of the need for these changes. These efforts are consistent with recent calls to use emerging data from IS and IR and precision medicine initiatives to drive health system improvement (213).

MAKING IS IN CRITICAL CARE EASIER AND MORE RELEVANT

IR is still gaining a foothold in critical care, as evidenced by recent calls to define the critical care IR agenda (10) and to bring IS and IR into the ICU (5). Many of the theories, models, and frameworks used in IS have been tested in behavioral health and outpatient care

settings rather than the fast-paced, high-stakes environment of the ICU. Efforts to apply IS principles to ICUs have been bolstered by the creation of critical care-specific IS training programs (214), recent published reviews in high-impact critical care journals highlighting IS methods to overcome barriers to the uptake of evidence-based practices (29, 124), and an increasing willingness by funding agencies, such as the U.S. National Institutes of Health, to fund IR in critical care (215). Moving forward, critical care IR can be made easier and more relevant by: 1) using established implementation frameworks, theories, and models (FTMs); 2) using hybrid effectiveness-implementation trials; 3) leveraging EHR data to inform and drive change; 4) linking implementation to QI efforts; and 5) using research and practice collaboratives. We explain each of these briefly below.

Use of Implementation Frameworks, Theories, and Models

Well-developed and empirically supported implementation FTMs enable the translation and adoption of evidence into daily clinical practice. Despite more than 100 FTMs relevant to IS (216), fewer than half (23–47%) of the published IS-based studies in clinical medicine used an FTM, including the underuse, superficial use (i.e., only citing a framework in the background or discussion sections), and/or misuse of FTMs, thus threatening the field's advancement (216). This observation is due in part to the difficulty in identifying and selecting FTMs appropriate to the problem at hand. Multiple published articles highlight how implementation FTMs may be used (28, 217, 218). Instead of developing new FTMs, the authors strongly recommend the selection and adaption (if needed) of existing FTMs in critical care IR. Using existing FTMs also helps to broaden the implementation evidence base and to standardize measurement, thereby allowing for comparisons across studies.

Use of Hybrid Effectiveness-Implementation Trials

Implementation outcomes such as "acceptability" and "fidelity" are fundamentally distinct from "classical" ICU outcomes of interest, including mortality, length of stay, and end-organ dysfunction (219). When evidence supporting an intervention's effectiveness is strong (e.g., multiple, large randomized controlled trials showing evidence of benefit), implementation studies may focus only on implementation outcomes. In critical care, intervention evidence is often based on randomized studies that may later be reversed (220) or on quasi-experimental studies demonstrating significant threats to inference. In these settings, it may be prudent to study both implementation and effectiveness simultaneously in an approach known as the "effectiveness-implementation hybrid design" (221), where relationships between implementation and effectiveness can be tested, and intervention effectiveness can be interrogated in clinical settings different from the original study.

Leveraging Electronic Health Records to Inform and Drive Change

IR tends to use mixed methods approaches to data collection in which both qualitative and quantitative data are used to characterize implementation determinants and evaluate implementation efforts. Collection of data are time-consuming, labor-intensive, and costly and may fall outside of the available resources for an implementation effort. The EHR is increasingly being used to facilitate clinical and health services research and QI efforts (222, 223). Linking patient-level EHR data to evidence-based protocols and presenting these data in easy-to-read formats can help facilitate real-time team decision-making support.

Data related to processes of care, such as nursing interventions documented in electronic flowsheets, could be leveraged to document performance gaps and to track the impact of implementation efforts on intervention compliance. Outcome measures related to the intervention can be evaluated over time and across ICU patient populations to assess the direct impacts on patients. Accessible, transparent, and provider-specific EHR-based performance and outcome data can help reduce practice variation and more rapidly drive unit-based change. Artificial intelligence and machine learning approaches could also be applied to identify patients at greatest risk of nosocomial complications (e.g., delirium), allowing implementers to concentrate their efforts on ICU patient populations most likely to benefit. EHRs can also be used as platforms for implementation strategies. For example, relevant guidelines can be presented to clinicians in the form of clinical decision support tools, ordering providers' choices can be constrained to conform with guidelines and/or evidence, and default orders can be engineered to "nudge" providers toward the desired care pattern (224).

Linking Implementation Efforts to Quality Improvement Initiatives

Health systems are focused on delivering high-quality care while constraining costs. For this reason, implementation efforts often compete with other programs for limited resources. But when implementation is aligned with existing quality initiatives, such as those directed by regulatory agencies and insurance payers, it is easier to make the "business case" for earmarking resources to support implementation. There are many evidence-based practices in critical care that are ripe for implementation. In selecting which best practices to focus on, linking efforts to the current priorities of the hospital or health system is often a useful approach (e.g., precision medicine initiatives, the Centers for Medicare & Medicaid Services Hospital Value-based Purchasing Program [22], and the Medicare Access and CHIP Reauthorization Act of 2015 [225]). Establishing this connection requires active engagement of ICU, hospital, and health system leaders in implementation efforts, to help garner needed resources, to make a strong financial case for implementation efforts, and to spread change across the organization.

Use of Research and Practice Collaboratives

As IR is contextual, the lessons learned from a local QI effort may or may not translate to other critical care settings. Ideally, IR and implementation practice teams could work together to identify common barriers and facilitators and to identify the most promising implementation strategies. The Society of Critical Care Medicine Discovery Network (226) is an example of a research network that can centralize institutional review board approval and data collection, facilitating multicenter IR studies that could help to advance critical care IS.

CONCLUSIONS

Significant delays in the widespread adoption of evidence-based critical care practices adversely affect patient outcomes and increase costs of care. IS and IR, along with their associated conceptual frameworks, provide a systematic approach to identifying effective strategies for overcoming barriers to the translation of evidence into critical

care practice. Effectively leveraging established implementation FTMs, hybrid effectiveness-implementation methods, EHR datasets, existing QI initiatives, and research and practice collaboratives can help to facilitate critical care IR. Using IS and IR to understand and address the causes and strategies for overcoming barriers can help improve the quality, safety, and value of care delivered to critically ill patients.

Acknowledgments

Dr. Barr received support for article research from the government; disclosed that she is a federal employee who works for the Veterans Health Administration. Dr. Kamdar's institution received funding from the National Institutes of Health (NIH). Drs. Kamdar, Ervin, Lane-Fall, and Liu received support for article research from the NIH. Dr. Lane-Fall's institution received funding from the NIH (grant number 1R01HL153735) and the Robert Wood Johnson Foundation; she received funding from the Anesthesia Patient Safety Foundation (Board of Directors). Dr. Liu's institution received funding from the NIH R35GM128672. The remaining authors have disclosed that they do not have any potential conflicts of interest.

REFERENCES

1. Corrigan J: Crossing the quality chasm. *In*: Building a Better Delivery System: A New Engineering/ Health Care Partnership. Reid PP, Compton WD, Grossman JH, et al. (Eds); National Academy of Engineering (US) and Institute of Medicine (US) Committee on Engineering and the Health Care System. Washington, DC, National Academies Press (US), 2005, pp 95–97
2. Kalassian KG, Dremsizov T, Angus DC: Translating research evidence into clinical practice: New challenges for critical care. Crit Care 2002; 6:11–14 [PubMed: 11940259]
3. Rhodes A, Evans LE, Alhazzani W, et al. : Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017; 43:304–377 [PubMed: 28101605]
4. Levy MM, Evans LE, Rhodes A: The surviving sepsis campaign bundle: 2018 update. Crit Care Med 2018; 46:997–1000 [PubMed: 29767636]
5. Kahn JM: Bringing implementation science to the intensive care unit. Curr Opin Crit Care 2017; 23:398–399 [PubMed: 28759467]
6. Haynes B, Haines A: Barriers and bridges to evidence based clinical practice. BMJ 1998; 317:273–276 [PubMed: 9677226]
7. Damschroder LJ, Aron DC, Keith RE, et al. : Fostering implementation of health services research findings into practice: A consolidated framework for advancing implementation science. Implement Sci 2009; 4:50 [PubMed: 19664226]
8. Beer M, Nohria N: Cracking the code of change. Harv Bus Rev 2000; 78:133–141, 216 [PubMed: 11183975]
9. Burnes B: Emergent change and planned change - competitors or allies? The case of XYZ construction. Int J Operations Production Management 2004; 24:886–902
10. Weiss CH, Krishnan JA, Au DH, et al. ; ATS Ad Hoc Committee on Implementation Science: An official American Thoracic Society research statement: Implementation science in pulmonary, critical care, and sleep medicine. Am J Respir Crit Care Med 2016; 194:1015–1025 [PubMed: 27739895]
11. Dearing J, Kee KF: Historical roots of dissemination and implementation science. In: Dissemination and Implementation Research in Health: Translating Science to Practice. Brownson, Colditz GA, Proctor EK (Eds). New York, NY, Oxford University Press, 2012, pp 55–71
12. Douglas NF, Burshnic VL: Implementation science: Tackling the research to practice gap in communication sciences and disorders. Perspectives of the ASHA Special Interest Groups 2019; 4:1–5
13. Olswang LB, Prelock PA: Bridging the gap between research and practice: Implementation science. J Speech Lang Hear Res 2015; 58:S1818–S1826 [PubMed: 26262822]
14. Greenhalgh T, Robert G, Macfarlane F, et al. : Diffusion of innovations in service organizations: Systematic review and recommendations. Milbank Q 2004; 82:581–629 [PubMed: 15595944]

15. Rogers EM: Diffusion of Innovations. New York, NY, Free Press of Glencoe, 1962
16. Weiss CH, Bucuvalas MJ: Social Science Research and Decision-Making. New York, NY, Columbia University Press, 1980
17. Weil MH: The Society of Critical Care Medicine, its history and its destiny. Crit Care Med 1973; 1:1–4 [PubMed: 4585934]
18. Weiss CH, Baker DW: The evolving application of implementation science in critical care*. Crit Care Med 2014; 42:996–997 [PubMed: 24633104]
19. Berwick DM, Nolan TW, Whittington J: The triple aim: Care, health, and cost. Health Aff (Millwood) 2008; 27:759–769 [PubMed: 18474969]
20. U.S. Department of Health & Human Services: About the Affordable Care Act. 2019. Available at: https://www.hhs.gov/healthcare/about-the-aca/index.html. Accessed October 28, 2020
21. Centers for Medicare & Medicaid Services: Accountable Care Organizations (ACOs). 2020. Available at: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ACO. Accessed October 28, 2020
22. Centers for Medicare & Medicaid Services: The Hospital Value-Based Purchasing (VBP) Program. 2020. Available at: https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/Value-Based-Programs/HVBP/Hospital-Value-Based-Purchasing. Accessed July 8, 2020
23. National Heart, Lung, and Blood Institute: Center for Translation Research and Implementation Science. 2019. Available at: https://www.nhlbi.nih.gov/about/divisions/center-translation-research-and-implementation-science. Accessed June 24, 2020
24. Marincola FM: Translational medicine: A two-way road. J Transl Med 2003; 1:1 [PubMed: 14527344]
25. Littman BH, Di Mario L, Plebani M, et al. : What's next in translational medicine? Clin Sci (Lond) 2007; 112:217–227 [PubMed: 17223795]
26. Rubio DM, Schoenbaum EE, Lee LS, et al. : Defining translational research: Implications for training. Acad Med 2010; 85:470–475 [PubMed: 20182120]
27. Thornicroft G, Lempp H, Tansella M: The place of implementation science in the translational medicine continuum. Psychol Med 2011; 41:2015–2021 [PubMed: 21320391]
28. Nilsen P: Making sense of implementation theories, models and frameworks. Implement Sci 2015; 10:53 [PubMed: 25895742]
29. Weiss CH: Why do we fail to deliver evidence-based practice in critical care medicine? Curr Opin Crit Care 2017; 23:400–405 [PubMed: 28858917]
30. Proctor EK, Powell BJ, Baumann AA, et al. : Writing implementation research grant proposals: Ten key ingredients. Implement Sci 2012; 7:96 [PubMed: 23062065]
31. Valente TW, Rogers EM: The origins and development of the diffusion of innovations paradigm as an example of scientific growth. Sci Commun 1995; 16:242–273 [PubMed: 12319357]
32. Kirk MA, Kelley C, Yankey N, et al. : A systematic review of the use of the consolidated framework for implementation research. Implement Sci 2016; 11:72 [PubMed: 27189233]
33. Norton WE, Kennedy AE, Chambers DA: Studying de-implementation in health: An analysis of funded research grants. Implement Sci 2017; 12:144 [PubMed: 29202782]
34. Fisher ES, Shortell SM, Savitz LA: Implementation science: A potential catalyst for delivery system reform. JAMA 2016; 315:339–340 [PubMed: 26813203]
35. Balas EA, Boren SA: Managing clinical knowledge for health care improvement. Yearb Med Inform 2000; 1:65–70
36. Grant J, Green L, Mason B: Basic research and health: A reassessment of the scientific basis for the support of biomedical science. Res Eval 2003; 12:217–224
37. Wratschko K: Empirical setting: The pharmaceutical industry. In: Strategic Orientation and Alliance Portfolio Configuration: The Interdependence of Strategy and Alliance Portfolio Management. Wiesbaden, Germany, Gabler, 2009, pp 87–96
38. Morris ZS, Wooding S, Grant J: The answer is 17 years, what is the question: Understanding time lags in translational research. J R Soc Med 2011; 104:510–520 [PubMed: 22179294]

39. Cook D, Guyatt G, Marshall J, et al. : A comparison of sucral-fate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. N Engl J Med 1998; 338:791–797 [PubMed: 9504939]
40. Young PJ, Bagshaw SM, Forbes AB, et al. : Effect of stress ulcer prophylaxis with proton pump inhibitors vs histamine-2 receptor blockers on in-hospital mortality among ICU patients receiving invasive mechanical ventilation: The PEPTIC Randomized Clinical Trial. JAMA 2020; 323:616–626 [PubMed: 31950977]
41. Drakulovic MB, Torres A, Bauer TT, et al. : Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: A randomised trial. Lancet 1999; 354:1851–1858 [PubMed: 10584721]
42. Keeley L: Reducing the risk of ventilator-acquired pneumonia through head of bed elevation. Nurs Crit Care 2007; 12:287–294 [PubMed: 17983363]
43. van Nieuwenhoven CA, Vandenbroucke-Grauls C, van Tiel FH, et al. : Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: A randomized study. Crit Care Med 2006; 34:396–402 [PubMed: 16424720]
44. Hébert PC, Wells G, Blajchman MA, et al. : A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999; 340:409–417 [PubMed: 9971864]
45. Hajjar LA, Vincent JL, Galas FR, et al. : Transfusion requirements after cardiac surgery: The TRACS randomized controlled trial. JAMA 2010; 304:1559–1567 [PubMed: 20940381]
46. Holst LB, Haase N, Wetterslev J, et al. ; TRISS Trial Group; Scandinavian Critical Care Trials Group: Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 2014; 371:1381–1391 [PubMed: 25270275]
47. Brower RG, Matthay MA, Morris A, et al. : Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342:1301–1308 [PubMed: 10793162]
48. Smulders K, van der Hoeven H, Weers-Pothoff I, et al. : A randomized clinical trial of intermittent subglottic secretion drainage in patients receiving mechanical ventilation. Chest 2002; 121:858–862 [PubMed: 11888973]
49. Lacherade JC, De Jonghe B, Guezennec P, et al. : Intermittent subglottic secretion drainage and ventilator-associated pneumonia: A multicenter trial. Am J Respir Crit Care Med 2010; 182:910–917 [PubMed: 20522796]
50. Damas P, Frippiat F, Ancion A, et al. : Prevention of ventilator-associated pneumonia and ventilator-associated conditions: A randomized controlled trial with subglottic secretion suctioning. Crit Care Med 2015; 43:22–30 [PubMed: 25343570]
51. Sandham JD, Hull RD, Brant RF, et al. ; Canadian Critical Care Clinical Trials Group: A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. N Engl J Med 2003; 348:5–14 [PubMed: 12510037]
52. Harvey S, Harrison DA, Singer M, et al. ; PAC-Man study collaboration: Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PACMan): A randomised controlled trial Lancet 2005; 366:472–477 [PubMed: 16084255]
53. Wheeler AP, Bernard GR, Thompson BT, et al. : Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl J Med 2006; 354:2213–2224 [PubMed: 16714768]
54. Nava S, Gregoretti C, Fanfulla F, et al. : Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med 2005; 33:2465–2470 [PubMed: 16276167]
55. Ferrer M, Valencia M, Nicolas JM, et al. : Early noninvasive ventilation averts extubation failure in patients at risk: A randomized trial. Am J Respir Crit Care Med 2006; 173:164–170 [PubMed: 16224108]
56. Ornico SR, Lobo SM, Sanches HS, et al. : Noninvasive ventilation immediately after extubation improves weaning outcome after acute respiratory failure: A randomized controlled trial. Crit Care 2013; 17:R39 [PubMed: 23497557]
57. Thille AW, Muller G, Gacouin A, et al. ; HIGH-WEAN Study Group and the REVA Research Network: Effect of postextubation high-flow nasal oxygen with noninvasive ventilation vs high-

flow nasal oxygen alone on reintubation among patients at high risk of extubation failure: A randomized clinical trial. JAMA 2019; 322:1465–1475 [PubMed: 31577036]

58. Pronovost P, Needham D, Berenholtz S, et al. : An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 2006; 355:2725–2732 [PubMed: 17192537]
59. Ely EW, Baker AM, Dunagan DP, et al. : Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med 1996; 335:1864–1869 [PubMed: 8948561]
60. Kress JP, Pohlman AS, O'Connor MF, et al. : Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000; 342:1471–1477 [PubMed: 10816184]
61. Girard TD, Kress JP, Fuchs BD, et al. : Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): A randomised controlled trial. Lancet 2008; 371:126–134 [PubMed: 18191684]
62. Morris PE, Goad A, Thompson C, et al. : Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med 2008; 36:2238–2243 [PubMed: 18596631]
63. Schweickert WD, Pohlman MC, Pohlman AS, et al. : Early physical and occupational therapy in mechanically ventilated, critically ill patients: A randomised controlled trial. Lancet 2009; 373:1874–1882 [PubMed: 19446324]
64. Schaller SJ, Anstey M, Blobner M, et al. ; International Early SOMS-guided Mobilization Research Initiative: Early, goal-directed mobilisation in the surgical intensive care unit: A randomised controlled trial. Lancet 2016; 388:1377–1388 [PubMed: 27707496]
65. Finfer S, Chittock DR, Su SY, et al. : Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009; 360:1283–1297 [PubMed: 19318384]
66. Casaer MP, Mesotten D, Hermans G, et al. : Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011; 365:506–517 [PubMed: 21714640]
67. Reignier J, Mercier E, Le Gouge A, et al. ; Clinical Research in Intensive Care and Sepsis (CRICS) Group: Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: A randomized controlled trial. JAMA 2013; 309:249–256 [PubMed: 23321763]
68. Guérin C, Reignier J, Richard JC, et al. ; PROSEVA Study Group: Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013; 368:2159–2168 [PubMed: 23688302]
69. Semler MW, Self WH, Wanderer JP, et al. ; SMART Investigators and the Pragmatic Critical Care Research Group: Balanced crystalloids versus saline in critically ill adults. N Engl J Med 2018; 378:829–839 [PubMed: 29485925]
70. Guo L, Xie J, Huang Y, et al. : Higher PEEP improves outcomes in ARDS patients with clinically objective positive oxygenation response to PEEP: A systematic review and meta-analysis. BMC Anesthesiol 2018; 18:172 [PubMed: 30447683]
71. Levy MM, Evans LE, Rhodes A: The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Med 2018; 44:925–928 [PubMed: 29675566]
72. Pun BT, Balas MC, Barnes-Daly MA, et al. : Caring for critically ill patients with the ABCDEF bundle: Results of the ICU liberation collaborative in over 15,000 adults. Crit Care Med 2019; 47:3–14 [PubMed: 30339549]
73. Arabi YM, Al-Hameed F, Burns KEA, et al. ; Saudi Critical Care Trials Group: Adjunctive intermittent pneumatic compression for venous thromboprophylaxis. N Engl J Med 2019; 380:1305–1315 [PubMed: 30779530]
74. Kaku S, Nguyen CD, Htet NN, et al. : Acute respiratory distress syndrome: Etiology, pathogenesis, and summary on management. J Intensive Care Med 2020; 35:723–737 [PubMed: 31208266]
75. Ashbaugh DG, Bigelow DB, Petty TL, et al. : Acute respiratory distress in adults. Lancet 1967; 2:319–323 [PubMed: 4143721]
76. Ferguson ND, Fan E, Camporota L, et al. : The Berlin definition of ARDS: An expanded rationale, justification, and supplementary material. Intensive Care Med 2012; 38:1573–1582 [PubMed: 22926653]
77. Hudson LD, Milberg JA, Anardi D, et al. : Clinical risks for development of the acute respiratory distress syndrome. Am J Respir Crit Care Med 1995; 151:293–301 [PubMed: 7842182]

78. Pepe PE, Potkin RT, Reus DH, et al. : Clinical predictors of the adult respiratory distress syndrome. Am J Surg 1982; 144:124–130 [PubMed: 7091520]

79. Katzenstein AL, Bloor CM, Leibow AA: Diffuse alveolar damage–the role of oxygen, shock, and related factors. A review. Am J Pathol 1976; 85:209–228 [PubMed: 788524]

80. Piantadosi CA, Schwartz DA: The acute respiratory distress syndrome. Ann Intern Med 2004; 141:460–470 [PubMed: 15381520]

81. Luhr OR, Antonsen K, Karlsson M, et al. : Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and Iceland. The ARF Study Group. Am J Respir Crit Care Med 1999; 159:1849–1861 [PubMed: 10351930]

82. Villar J: What is the acute respiratory distress syndrome? Respir Care 2011; 56:1539–1545 [PubMed: 22008395]

83. Bersten AD, Edibam C, Hunt T, et al. ; Australian and New Zealand Intensive Care Society Clinical Trials Group: Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian States. Am J Respir Crit Care Med 2002; 165:443–448 [PubMed: 11850334]

84. Bellani G, Laffey JG, Pham T, et al. ; LUNG SAFE Investigators; ESICM Trials Group: Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016; 315:788–800 [PubMed: 26903337]

85. Stapleton RD, Wang BM, Hudson LD, et al. : Causes and timing of death in patients with ARDS. Chest 2005; 128:525–532 [PubMed: 16100134]

86. Erickson SE, Martin GS, Davis JL, et al. ; NIH NHLBI ARDS Network: Recent trends in acute lung injury mortality: 1996–2005. Crit Care Med 2009; 37:1574–1579 [PubMed: 19325464]

87. Rubenfeld GD, Caldwell E, Peabody E, et al. : Incidence and outcomes of acute lung injury. N Engl J Med 2005; 353:1685–1693 [PubMed: 16236739]

88. Artigas A, Bernard GR, Carlet J, et al. : The American-European Consensus Conference on ARDS, part 2. Ventilatory, pharmacologic, supportive therapy, study design strategies and issues related to recovery and remodeling. Intensive Care Med 1998; 24:378–398 [PubMed: 9609420]

89. Ranieri VM, Suter PM, Tortorella C, et al. : Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: A randomized controlled trial. JAMA 1999; 282:54–61 [PubMed: 10404912]

90. Serpa Neto A, Cardoso SO, Manetta JA, et al. : Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: A meta-analysis. JAMA 2012; 308:1651–1659 [PubMed: 23093163]

91. Neto AS, Simonis FD, Barbas CS, et al. ; PROtective Ventilation Network Investigators: Lung-protective ventilation with low tidal volumes and the occurrence of pulmonary complications in patients without acute respiratory distress syndrome: A systematic review and individual patient data analysis. Crit Care Med 2015; 43:2155–2163 [PubMed: 26181219]

92. Fuller BM, Mohr NM, Drewry AM, et al. : Lower tidal volume at initiation of mechanical ventilation may reduce progression to acute respiratory distress syndrome: A systematic review. Crit Care 2013; 17:R11 [PubMed: 23331507]

93. Putensen C, Theuerkauf N, Zinserling J, et al. : Meta-analysis: Ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. Ann Intern Med 2009; 151:566–576 [PubMed: 19841457]

94. Petrucci N, Iacovelli W: Lung protective ventilation strategy for the acute respiratory distress syndrome. Cochrane Database Syst Rev 2017; 2017:Cd003844

95. Bhattacharjee S, Soni KD, Maitra S: Recruitment maneuver does not provide any mortality benefit over lung protective strategy ventilation in adult patients with acute respiratory distress syndrome: A meta-analysis and systematic review of the randomized controlled trials. J Intensive Care 2018; 6:35 [PubMed: 29983985]

96. Fan E, Del Sorbo L, Goligher EC, et al. ; American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine: An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical

Practice Guideline: Mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2017; 195:1253–1263 [PubMed: 28459336]

97. Spece LJ, Mitchell KH, Caldwell ES, et al. : Low tidal volume ventilation use remains low in patients with acute respiratory distress syndrome at a single center. J Crit Care 2018; 44:72–76 [PubMed: 29073535]
98. Walkey AJ, Wiener RS: Risk factors for underuse of lung-protective ventilation in acute lung injury. J Crit Care 2012; 27:323.e1–e9
99. Umoh NJ, Fan E, Mendez-Tellez PA, et al. : Patient and intensive care unit organizational factors associated with low tidal volume ventilation in acute lung injury. Crit Care Med 2008; 36:1463–1468 [PubMed: 18434907]
100. Rubenfeld GD, Cooper C, Carter G, et al. : Barriers to providing lung-protective ventilation to patients with acute lung injury. Crit Care Med 2004; 32:1289–1293 [PubMed: 15187508]
101. Dennison CR, Mendez-Tellez PA, Wang W, et al. : Barriers to low tidal volume ventilation in acute respiratory distress syndrome: Survey development, validation, and results. Crit Care Med 2007; 35:2747–2754 [PubMed: 17901838]
102. Kalhan R, Mikkelsen M, Dedhiya P, et al. : Underuse of lung protective ventilation: Analysis of potential factors to explain physician behavior. Crit Care Med 2006; 34:300–306 [PubMed: 16424706]
103. Sjoding MW: Translating evidence into practice in acute respiratory distress syndrome: Teamwork, clinical decision support, and behavioral economic interventions. Curr Opin Crit Care 2017; 23:406–411 [PubMed: 28742539]
104. Cavalcanti AB, Bozza FA, Machado FR, et al. : Effect of a quality improvement intervention with daily round checklists, goal setting, and clinician prompting on mortality of critically ill patients: A randomized clinical trial. JAMA 2016; 315:1480–1490 [PubMed: 27115264]
105. O'Grady NP, Alexander M, Burns LA, et al. ; Healthcare Infection Control Practices Advisory Committee: Guidelines for the prevention of intravascular catheter-related infections. Am J Infect Control 2011; 39:S1–S34 [PubMed: 21511081]
106. Mermel LA: Prevention of intravascular catheter-related infections. Ann Intern Med 2000; 132:391–402 [PubMed: 10691590]
107. Marschall J, Mermel LA, Classen D, et al. : Strategies to prevent central line-associated bloodstream infections in acute care hospitals. Infect Control Hosp Epidemiol 2008; 29(Suppl 1):S22–S30 [PubMed: 18840085]
108. O'Grady NP, Alexander M, Burns LA, et al. : Healthcare Infection Control Practices Advisory Committee (HICPAC). Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis 2011; 52:e162–e193 [PubMed: 21460264]
109. Marschall J, Mermel LA, Fakih M, et al. ; Society for Healthcare Epidemiology of America: Strategies to prevent central line-associated bloodstream infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014; 35:753–771 [PubMed: 24915204]
110. Rosenthal MB: Nonpayment for performance? Medicare's new reimbursement rule. N Engl J Med 2007; 357:1573–1575 [PubMed: 17942869]
111. Ista E, van der Hoven B, Kornelisse RF, et al. : Effectiveness of insertion and maintenance bundles to prevent central-line-associated bloodstream infections in critically ill patients of all ages: A systematic review and meta-analysis. Lancet Infect Dis 2016; 16:724–734 [PubMed: 26907734]
112. Dixon-Woods M, Leslie M, Tarrant C, et al. : Explaining matching Michigan: An ethnographic study of a patient safety program. Implement Sci 2013; 8:70 [PubMed: 23786847]
113. Furuya EY, Dick AW, Herzig CT, et al. : Central line-associated bloodstream infection reduction and bundle compliance in intensive care units: A national study. Infect Control Hosp Epidemiol 2016; 37:805–810 [PubMed: 27052993]
114. Strickler S, Gupta RR, Doucette JT, et al. : A quality assurance investigation of CLABSI events: Are there exceptions to never? J Infect Prev 2018; 19:22–28 [PubMed: 29317911]
115. Zingg W, Walder B, Pittet D: Prevention of catheter-related infection: Toward zero risk? Curr Opin Infect Dis 2011; 24:377–384 [PubMed: 21587071]

116. Bell T, O'Grady NP: Prevention of central line-associated bloodstream infections. Infect Dis Clin North Am 2017; 31:551–559 [PubMed: 28687213]

117. Barr J, Fraser GL, Puntillo K, et al. ; American College of Critical Care Medicine: Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013; 41: 263–306 [PubMed: 23269131]

118. Devlin JW, Skrobik Y, Gélinas C, et al. : Clinical practice guidelines for the prevention and management of pain, agitation/ sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med 2018; 46:e825–e873 [PubMed: 30113379]

119. Barnes-Daly MA, Phillips G, Ely EW: Improving hospital survival and reducing brain dysfunction at seven california community hospitals: Implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. Crit Care Med 2017; 45:171–178 [PubMed: 27861180]

120. Society of Critical Care Medicine: ICU Liberation Bundle (A-F). 2020. Available at: https://www.sccm.org/ICULiberation/ABCDEF-Bundles. Accessed June 24, 2020

121. Hsieh SJ, Otusanya O, Gershengorn HB, et al. : Staged implementation of awakening and breathing, coordination, delirium monitoring and management, and early mobilization bundle improves patient outcomes and reduces hospital costs. Crit Care Med 2019; 47:885–893 [PubMed: 30985390]

122. Ervin JN, Rentes VC, Dibble ER, et al. : Evidence-based practices for acute respiratory failure and acute respiratory distress syndrome: A systematic review of reviews. Chest 2020; 158:2381–2393 [PubMed: 32682771]

123. Ely EW: The ABCDEF bundle: Science and philosophy of how ICU liberation serves patients and families. Crit Care Med 2017; 45:321–330 [PubMed: 28098628]

124. Costa DK, White MR, Ginier E, et al. : Identifying barriers to delivering the awakening and breathing coordination, delirium, and early exercise/mobility bundle to minimize adverse outcomes for mechanically ventilated patients: A systematic review. Chest 2017; 152:304–311 [PubMed: 28438605]

125. Miller MA, Govindan S, Watson SR, et al. : ABCDE, but in that order? A cross-sectional survey of Michigan intensive care unit sedation, delirium, and early mobility practices. Ann Am Thorac Soc 2015; 12:1066–1071 [PubMed: 25970737]

126. Morandi A, Piva S, Ely EW, et al. : Worldwide survey of the "Assessing Pain, Both Spontaneous Awakening and Breathing Trials, Choice of Drugs, Delirium Monitoring/Management, Early Exercise/Mobility, and Family Empowerment" (ABCDEF) bundle. Crit Care Med 2017; 45:e1111–e1122 [PubMed: 28787293]

127. Jolley SE, Regan-Baggs J, Dickson RP, et al. : Medical intensive care unit clinician attitudes and perceived barriers towards early mobilization of critically ill patients: A cross-sectional survey study. BMC Anesthesiol 2014; 14:84 [PubMed: 25309124]

128. Baggs JG, Schmitt MH, Mushlin AI, et al. : Association between nurse-physician collaboration and patient outcomes in three intensive care units. Crit Care Med 1999; 27:1991–1998 [PubMed: 10507630]

129. Bakhru RN, McWilliams DJ, Wiebe DJ, et al. : Intensive care unit structure variation and implications for early mobilization practices. An international survey. Ann Am Thorac Soc 2016; 13:1527–1537 [PubMed: 27268952]

130. Balas MC, Burke WJ, Gannon D, et al. : Implementing the awakening and breathing coordination, delirium monitoring/ management, and early exercise/mobility bundle into everyday care: Opportunities, challenges, and lessons learned for implementing the ICU Pain, Agitation, and Delirium Guidelines. Crit Care Med 2013; 41:S116–S127 [PubMed: 23989089]

131. Balas MC, Pun BT, Pasero C, et al. : Common challenges to effective ABCDEF bundle implementation: The ICU liberation campaign experience. Crit Care Nurse 2019; 39:46–60 [PubMed: 30710036]

132. Carrothers KM, Barr J, Spurlock B, et al. : Contextual issues influencing implementation and outcomes associated with an integrated approach to managing pain, agitation, and delirium in adult ICUs. Crit Care Med 2013; 41:S128–S135 [PubMed: 23989090]

133. Connolly B, O'Neill B, Salisbury L, et al. ; Enhanced Recovery After Critical Illness Programme Group: Physical rehabilitation interventions for adult patients during critical illness: An overview of systematic reviews. Thorax 2016; 71:881–890 [PubMed: 27220357]

134. Barr J, Ghaferi AA, Costa DK, et al. : Organizational characteristics associated with ICU liberation (ABCDEF) bundle implementation by adult ICUs in Michigan. Crit Care Explor 2020; 2:e0169 [PubMed: 32885171]

135. Krein SL, Damschroder LJ, Kowalski CP, et al. : The influence of organizational context on quality improvement and patient safety efforts in infection prevention: A multi-center qualitative study. Soc Sci Med 2010; 71:1692–1701 [PubMed: 20850918]

136. Pronovost PJ, Berenholtz SM, Goeschel C, et al. : Improving patient safety in intensive care units in Michigan. J Crit Care 2008; 23:207–221 [PubMed: 18538214]

137. Dubb R, Nydahl P, Hermes C, et al. : Barriers and strategies for early mobilization of patients in intensive care units. Ann Am Thorac Soc 2016; 13:724–730 [PubMed: 27144796]

138. Boltey EM, Iwashyna TJ, Hyzy RC, et al. : Ability to predict team members' behaviors in ICU teams is associated with routine ABCDE implementation. J Crit Care 2019; 51:192–197 [PubMed: 30856524]

139. Costa DK, Valley TS, Miller MA, et al. : ICU team composition and its association with ABCDE implementation in a quality collaborative. J Crit Care 2018; 44:1–6 [PubMed: 28978488]

140. Brummel NE, Vasilevskis EE, Han JH, et al. : Implementing delirium screening in the ICU: Secrets to success. Crit Care Med 2013; 41:2196–2208 [PubMed: 23896832]

141. Pun BT, Devlin JW: Delirium monitoring in the ICU: Strategies for initiating and sustaining screening efforts. Semin Respir Crit Care Med 2013; 34:179–188 [PubMed: 23716309]

142. Davidson JE, Aslakson RA, Long AC, et al. : Guidelines for family-centered care in the neonatal, pediatric, and adult ICU. Crit Care Med 2017; 45:103–128 [PubMed: 27984278]

143. Society of Critical Care Medicine: Family Engagement and Empowerment. 2020. Available at: https://www.sccm.org/ICULiberation/ABCDEF-Bundles/Family-Engagement. Accessed June 24, 2020

144. Barnes-Daly MA, Pun BT, Harmon LA, et al. : Improving health care for critically ill patients using an evidence-based collaborative approach to ABCDEF bundle dissemination and implementation. Worldviews Evid Based Nurs 2018; 15:206–216 [PubMed: 29729659]

145. Barnes-Daly MA: Using an interprofessional team approach to implement evidence-based practice. In: ICU Liberation: The Power of Pain Control, Minimal Sedation, and Early Mobility. Balas M, Clemmer T, Hargett K (Eds). Mount Prospect, IL, Society of Critical Care Medicine, 2015, pp 127–134

146. Muche-Borowski C, Nothacker M, Kopp I: [Implementation of clinical practice guidelines: How can we close the evidence-practice gap?]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2015; 58:32–37 [PubMed: 25412582]

147. Society of Critical Care Medicine: Improving Patient Care Through the ICU Liberation Campaign. Critical Connections 2019. 2020. Available at: https://www.sccm.org/Communications/Critical-Connections/Archives/2019/Improving-Patient-Care-Through-the-ICU-Liberation. Accessed July 7, 2020

148. Gordon and Betty Moore Foundation: Society for Critical Care Medicine's ICU Liberation Campaign Launches New Initiative. 2015. Available at: https://www.moore.org/article-detail?newsUrlName=society-for-critical-care-medicines-icu-liberation-campaign-launches-new-initiative. Accessed July 7, 2020

149. Vanderbilt University: Project REDCap. 2020. Available at: https://www.project-redcap.org/. Accessed July 7, 2020

150. Stollings JL, Devlin JW, Pun BT, et al. : Implementing the ABCDEF bundle: Top 8 questions asked during the ICU liberation ABCDEF bundle improvement collaborative. Crit Care Nurse 2019; 39:36–45 [PubMed: 30710035]

151. Stollings JL, Devlin JW, Lin JC, et al. : Best practices for conducting interprofessional team rounds to facilitate performance of the ICU liberation (ABCDEF) bundle. Crit Care Med 2020; 48:562–570 [PubMed: 32205603]

152. Hoesing H; Joint Commission International: Clinical Practice Guidelines: Closing the Gap Between Theory and Practice. 2016. Available at: https://www.elsevier.com/__data/assets/pdf_file/0007/190177/JCI-Whitepaper_cpgs-closing-the-gap.pdf. Accessed July 7, 2020
153. Society of Critical Care Medicine: Family Engagement and Empowerment. 2020. Available at: https://www.sccm.org/ICULiberation/ABCDEF-Bundles/Family-Engagement. Accessed July 7, 2020
154. Collinsworth AW, Masica AL, Priest EL, et al. : Modifying the electronic health record to facilitate the implementation and evaluation of a bundled care program for intensive care unit delirium. EGEMS (Wash DC) 2014; 2:1121 [PubMed: 25848599]
155. Krumholz HM: Post-hospital syndrome–an acquired, transient condition of generalized risk. N Engl J Med 2013; 368:100–102 [PubMed: 23301730]
156. Covinsky KE, Pierluissi E, Johnston CB: Hospitalization-associated disability: "She was probably able to ambulate, but I'm not sure." JAMA 2011; 306:1782–1793 [PubMed: 22028354]
157. Needham DM, Davidson J, Cohen H, et al. : Improving long-term outcomes after discharge from intensive care unit: Report from a stakeholders' conference. Crit Care Med 2012; 40:502–509 [PubMed: 21946660]
158. Wunsch H, Guerra C, Barnato AE, et al. : Three-year outcomes for Medicare beneficiaries who survive intensive care. JAMA 2010; 303:849–856 [PubMed: 20197531]
159. Cuthbertson BH, Roughton S, Jenkinson D, et al. : Quality of life in the five years after intensive care: A cohort study. Crit Care 2010; 14:R6 [PubMed: 20089197]
160. Crawford B, Skeath M, Whippy A: Multifocal clinical performance improvement across 21 hospitals. J Healthc Qual 2015; 37:117–125 [PubMed: 26247072]
161. Schmittdiel JA, Dlott R, Young JD, et al. : The delivery science rapid analysis program: A research and operational partnership at Kaiser Permanente Northern California. Learn Health Syst 2017; 1:e10035 [PubMed: 29152588]
162. Grant RW, Schmittdiel JA: Building a career as a delivery science researcher in a changing health care landscape. J Gen Intern Med 2015; 30:880–882 [PubMed: 25591970]
163. Lieu TA, Madvig PR: Strategies for building delivery science in an integrated health care system. J Gen Intern Med 2019; 34:1043–1047 [PubMed: 30684194]
164. Lieu TA, Platt R: Applied research and development in health care - time for a frameshift. N Engl J Med 2017; 376:710–713 [PubMed: 28225671]
165. Liu VX, Morehouse JW, Baker JM, et al. : Data that drive: Closing the loop in the learning hospital system. J Hosp Med 2016; 11(Suppl 1):S11–S17 [PubMed: 27805797]
166. Whippy A, Skeath M, Crawford B, et al. : Kaiser Permanente's performance improvement system, part 3: Multisite improvements in care for patients with sepsis. Jt Comm J Qual Patient Saf 2011; 37:483–493 [PubMed: 22132659]
167. Liu V, Escobar GJ, Greene JD, et al. : Hospital deaths in patients with sepsis from 2 independent cohorts. JAMA 2014; 312:90–92 [PubMed: 24838355]
168. Liu V, Lei X, Prescott HC, et al. : Hospital readmission and healthcare utilization following sepsis in community settings. J Hosp Med 2014; 9:502–507 [PubMed: 24700730]
169. Liu V, Morehouse JW, Soule J, et al. : Fluid volume, lactate values, and mortality in sepsis patients with intermediate lactate values. Ann Am Thorac Soc 2013; 10:466–473 [PubMed: 24004068]
170. Liu VX, Fielding-Singh V, Greene JD, et al. : The timing of early antibiotics and hospital mortality in sepsis. Am J Respir Crit Care Med 2017; 196:856–863 [PubMed: 28345952]
171. Liu VX, Morehouse JW, Marelich GP, et al. : Multicenter implementation of a treatment bundle for patients with sepsis and intermediate lactate values. Am J Respir Crit Care Med 2016; 193:1264–1270 [PubMed: 26695114]
172. Schuler A, Wulf DA, Lu Y, et al. : The impact of acute organ dysfunction on long-term survival in sepsis. Crit Care Med 2018; 46:843–849 [PubMed: 29432349]
173. Seymour CW, Rosengart MR: Septic shock: Advances in diagnosis and treatment. JAMA 2015; 314:708–717 [PubMed: 26284722]

174. Liu VX, Escobar GJ, Chaudhary R, et al. : Healthcare utilization and infection in the week prior to sepsis hospitalization. Crit Care Med 2018; 46:513–516 [PubMed: 29309371]

175. Liu V, Clark MP, Mendoza M, et al. : Automated identification of pneumonia in chest radiograph reports in critically ill patients. BMC Med Inform Decis Mak 2013; 13:90 [PubMed: 23947340]

176. Escobar GJ, Baker JM, Kipnis P, et al. : Prediction of recurrent Clostridium difficile infection using comprehensive electronic medical records in an integrated healthcare delivery system. Infect Control Hosp Epidemiol 2017; 38:1196–1203 [PubMed: 28835289]

177. Liu V, Herbert D, Foss-Durant A, et al. : Evaluation following staggered implementation of the "Rethinking Critical Care" ICU care bundle in a multicenter community setting. Crit Care Med 2016; 44:460–467 [PubMed: 26540402]

178. Angel C, Brooks K, Fourie J: Standardizing management of adults with delirium hospitalized on medical-surgical units. Perm J 2016; 20:16–002

179. LaHue SC, Douglas VC, Kuo T, et al. : Association between inpatient delirium and hospital readmission in patients ≥ 65 years of age: A retrospective cohort study. J Hosp Med 2019; 14:201–206 [PubMed: 30933669]

180. Liu VX, Rosas E, Hwang J, et al. : Enhanced recovery after surgery program implementation in 2 surgical populations in an integrated health care delivery system. JAMA Surg 2017; 152:e171032 [PubMed: 28492816]

181. Liu VX, Rosas E, Hwang JC, et al. : The Kaiser Permanente Northern California enhanced recovery after surgery program: Design, development, and implementation. Perm J 2017; 21:17–003

182. Liu VX, Eaton A, Lee DC, et al. : Postoperative opioid use before and after enhanced recovery after surgery program implementation. Ann Surg 2019; 270:e69–e71 [PubMed: 31232786]

183. Nguyen-Huynh MN, Klingman JG, Avins AL, et al. ; KPNC Stroke FORCE Team: Novel telestroke program improves thrombolysis for acute stroke across 21 hospitals of an integrated healthcare system. Stroke 2018; 49:133–139 [PubMed: 29247142]

184. Roubinian NH, Plimier C, Woo JP, et al. : Effect of donor, component, and recipient characteristics on hemoglobin increments following red blood cell transfusion. Blood 2019; 134:1003–1013 [PubMed: 31350268]

185. Roubinian NH, Murphy EL, Mark DG, et al. : Long-term outcomes among patients discharged from the hospital with moderate anemia: A retrospective cohort study. Ann Intern Med 2019; 170:81–89 [PubMed: 30557414]

186. Roubinian NH, Escobar GJ, Liu V, et al. ; NHLBI Recipient Epidemiology and Donor Evaluation Study (REDS-III): Decreased red blood cell use and mortality in hospitalized patients. JAMA Intern Med 2014; 174:1405–1407 [PubMed: 24978650]

187. Hedderson M, Lee D, Hunt E, et al. : Enhanced recovery after surgery to change process measures and reduce opioid use after cesarean delivery: A quality improvement initiative. Obstet Gynecol 2019; 134:511–519 [PubMed: 31403591]

188. Kim YS, Escobar GJ, Halpern SD, et al. : The natural history of changes in preferences for life-sustaining treatments and implications for inpatient mortality in younger and older hospitalized adults. J Am Geriatr Soc 2016; 64:981–989 [PubMed: 27119583]

189. Escobar GJ, Ragins A, Scheirer P, et al. : Nonelective rehospitalizations and postdischarge mortality: Predictive models suitable for use in real time. Med Care 2015; 53:916–923 [PubMed: 26465120]

190. Granich R, Sutton Z, Kim YS, et al. : Early detection of critical illness outside the intensive care unit: Clarifying treatment plans and honoring goals of care using a supportive care team. J Hosp Med 2016; 11(Suppl 1):S40–S47 [PubMed: 27805799]

191. Kipnis P, Turk BJ, Wulf DA, et al. : Development and validation of an electronic medical record-based alert score for detection of inpatient deterioration outside the ICU. J Biomed Inform 2016; 64:10–19 [PubMed: 27658885]

192. Dummett BA, Adams C, Scruth E, et al. : Incorporating an early detection system into routine clinical practice in two community hospitals. J Hosp Med 2016; 11(Suppl 1):S25–S31 [PubMed: 27805798]

193. Escobar GJ, LaGuardia JC, Turk BJ, et al. : Early detection of impending physiologic deterioration among patients who are not in intensive care: Development of predictive models using data from an automated electronic medical record. J Hosp Med 2012; 7:388–395 [PubMed: 22447632]

194. Ajzen I: The theory of planned behavior. Organ Behav Hum Decis Process 1991; 50:179–211

195. Cane J, O'Connor D, Michie S: Validation of the theoretical domains framework for use in behaviour change and implementation research. Implement Sci 2012; 7:37 [PubMed: 22530986]

196. Reader TW, Flin R, Mearns K, et al. : Developing a team performance framework for the intensive care unit. Crit Care Med 2009; 37:1787–1793 [PubMed: 19325474]

197. Weiner BJ, Lewis MA, Linnan LA: Using organization theory to understand the determinants of effective implementation of worksite health promotion programs. Health Educ Res 2009; 24:292–305 [PubMed: 18469319]

198. McLeroy KR, Bibeau D, Steckler A, et al. : An ecological perspective on health promotion programs. Health Educ Q 1988; 15:351–377 [PubMed: 3068205]

199. Tabak RG, Khoong EC, Chambers DA, et al. : Bridging research and practice: Models for dissemination and implementation research. Am J Prev Med 2012; 43:337–350 [PubMed: 22898128]

200. Proctor EK, Landsverk J, Aarons G, et al. : Implementation research in mental health services: An emerging science with conceptual, methodological, and training challenges. Adm Policy Ment Health 2009; 36:24–34 [PubMed: 19104929]

201. Powell BJ, Waltz TJ, Chinman MJ, et al. : A refined compilation of implementation strategies: Results from the Expert Recommendations for Implementing Change (ERIC) project. Implement Sci 2015; 10:21 [PubMed: 25889199]

202. Kirchner JE, Powell BJ, Smith JL, et al.: Implementation strategies. In: Dissemination and Implementation Research in Health: Translating Science to Practice. Brownson RC, Colditz GA, Proctor EK (Eds). New York, NY, Oxford University Press, 2018, pp 245–266

203. Michie S, Atkins L, West R: The Behaviour Change Wheel—A Guide to Designing Interventions. Great Britain, Silverback Publishing, 2014

204. Fernandez ME, Ten Hoor GA, van Lieshout S, et al. : Implementation mapping: Using intervention mapping to develop implementation strategies. Front Public Health 2019; 7:158 [PubMed: 31275915]

205. Powell BJ, Beidas RS, Lewis CC, et al. : Methods to improve the selection and tailoring of implementation strategies. J Behav Health Serv Res 2017; 44:177–194 [PubMed: 26289563]

206. Ervin JN, Kahn JM, Cohen TR, et al. : Teamwork in the intensive care unit. Am Psychol 2018; 73:468–477 [PubMed: 29792461]

207. Manthous C, Nembhard IM, Hollingshead AB: Building effective critical care teams. Crit Care 2011; 15:307 [PubMed: 21884639]

208. Manthous CA, Hollingshead AB: Team science and critical care. Am J Respir Crit Care Med 2011; 184:17–25 [PubMed: 21471081]

209. Aitken LM, Hackwood B, Crouch S, et al. : Creating an environment to implement and sustain evidence based practice: A developmental process. Aust Crit Care 2011; 24:244–254 [PubMed: 21295994]

210. Lusardi P: So you want to change practice: Recognizing practice issues and channeling those ideas. Crit Care Nurse 2012; 32:55–64

211. Maxwell M, Murphy K, McGettigan M: Changing ICU culture to reduce catheter-associated urinary tract infections. Can J Infect Control 2018; 33:39–43

212. Kleinpell R, Zimmerman J, Vermoch KL, et al. : Promoting family engagement in the ICU: Experience from a national collaborative of 63 ICUs. Crit Care Med 2019; 47:1692–1698 [PubMed: 31567354]

213. Chambers DA, Feero WG, Khoury MJ: Convergence of implementation science, precision medicine, and the learning health care system: A new model for biomedical research. JAMA 2016; 315:1941–1942 [PubMed: 27163980]

214. Institute for Healthcare Policy and Innovation: Training to Advance Care Through Implementation Science in Cardiac and Lung Illnesses. 2020. Available at: https://ihpi.umich.edu/education-training/education-training/programs/tactical. Accessed July 8, 2020

215. National Heart, Lung, and Blood Institute: NHLBI Workshop on Implementation Science in Critical Care. 2016. Available at: https://www.nhlbi.nih.gov/events/2016/nhlbi-workshop-implementation-science-critical-care. Accessed July 8, 2020

216. Birken SA, Powell BJ, Shea CM, et al. : Criteria for selecting implementation science theories and frameworks: Results from an international survey. Implement Sci 2017; 12:124 [PubMed: 29084566]

217. Wensing M, Grol R: Knowledge translation in health: How implementation science could contribute more. BMC Med 2019; 17:88 [PubMed: 31064388]

218. Damschroder LJ: Clarity out of chaos: Use of theory in implementation research. Psychiatry Res 2020; 283:112461 [PubMed: 31257020]

219. Proctor E, Silmere H, Raghavan R, et al. : Outcomes for implementation research: Conceptual distinctions, measurement challenges, and research agenda. Adm Policy Ment Health 2011; 38:65–76 [PubMed: 20957426]

220. Niven DJ, McCormick TJ, Straus SE, et al. : Reproducibility of clinical research in critical care: A scoping review. BMC Med 2018; 16:26 [PubMed: 29463308]

221. Curran GM, Bauer M, Mittman B, et al. : Effectiveness-implementation hybrid designs: Combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care 2012; 50:217–226 [PubMed: 22310560]

222. Cowie MR, Blomster JI, Curtis LH, et al. : Electronic health records to facilitate clinical research. Clin Res Cardiol 2017; 106:1–9

223. Casey JA, Schwartz BS, Stewart WF, et al. : Using electronic health records for population health research: A review of methods and applications. Annu Rev Public Health 2016; 37:61–81 [PubMed: 26667605]

224. Patel MS, Day SC, Halpern SD, et al. : Generic medication prescription rates after health system-wide redesign of default options within the electronic health record. JAMA Intern Med 2016; 176:847–848 [PubMed: 27159011]

225. Centers for Medicare & Medicaid Services: MACRA. 2020. Available at: https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/Value-Based-Programs/MACRA-MIPS-and-APMs/MACRA-MIPS-and-APMs. Accessed July 8, 2020

226. Society of Critical Care Medicine: Discovery, the Critical Care Research Network. 2020. Available at: https://www.sccm.org/Research/Research/Discovery-Research-Network. Accessed July 8, 2020

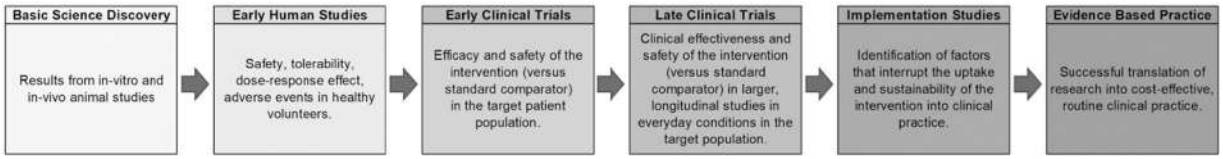

Figure 1.
Implementation research on the continuum of evidence-based practice.

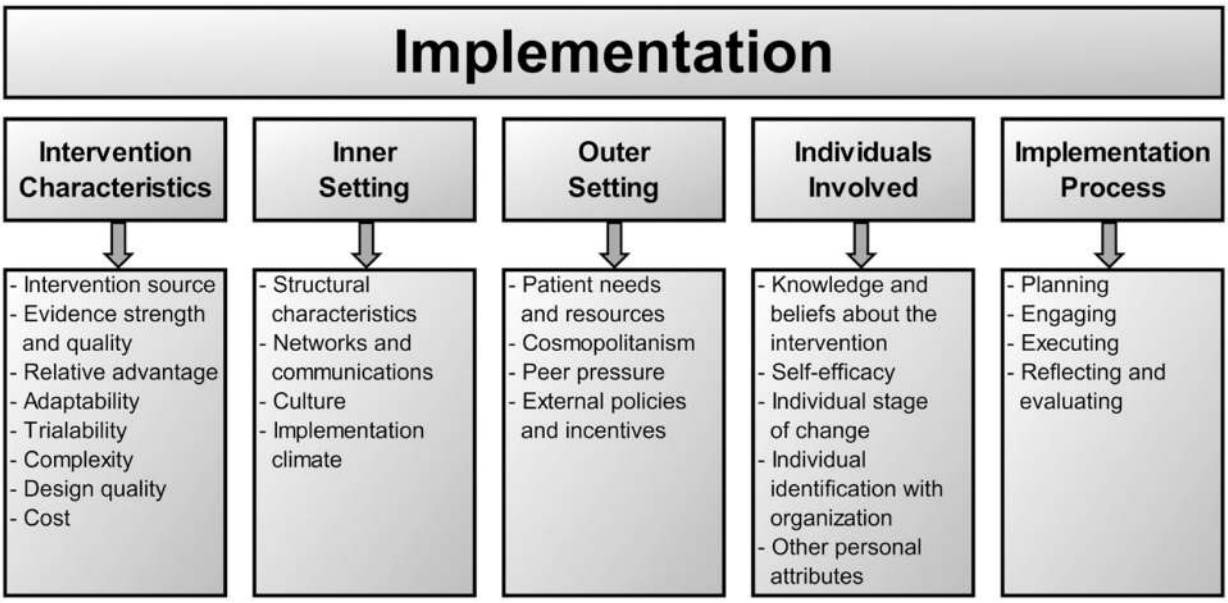

Figure 2.
Consolidated framework for implementation research (7).

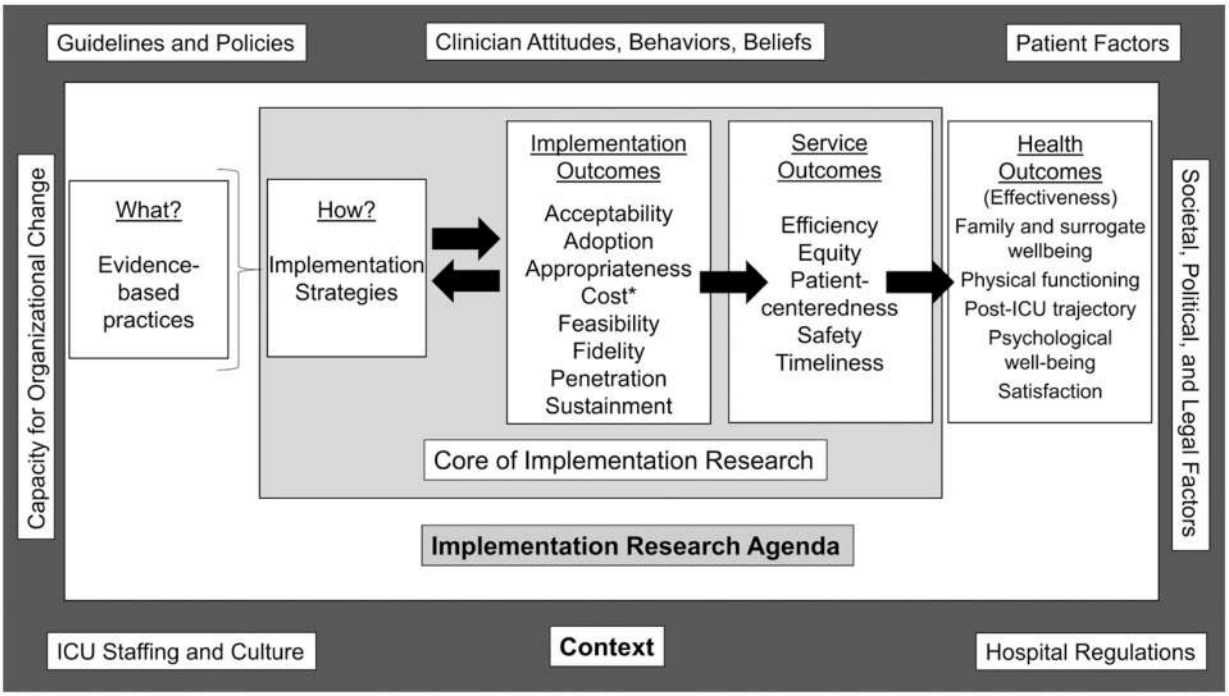

Figure 3.
Conceptual model for implementation research.

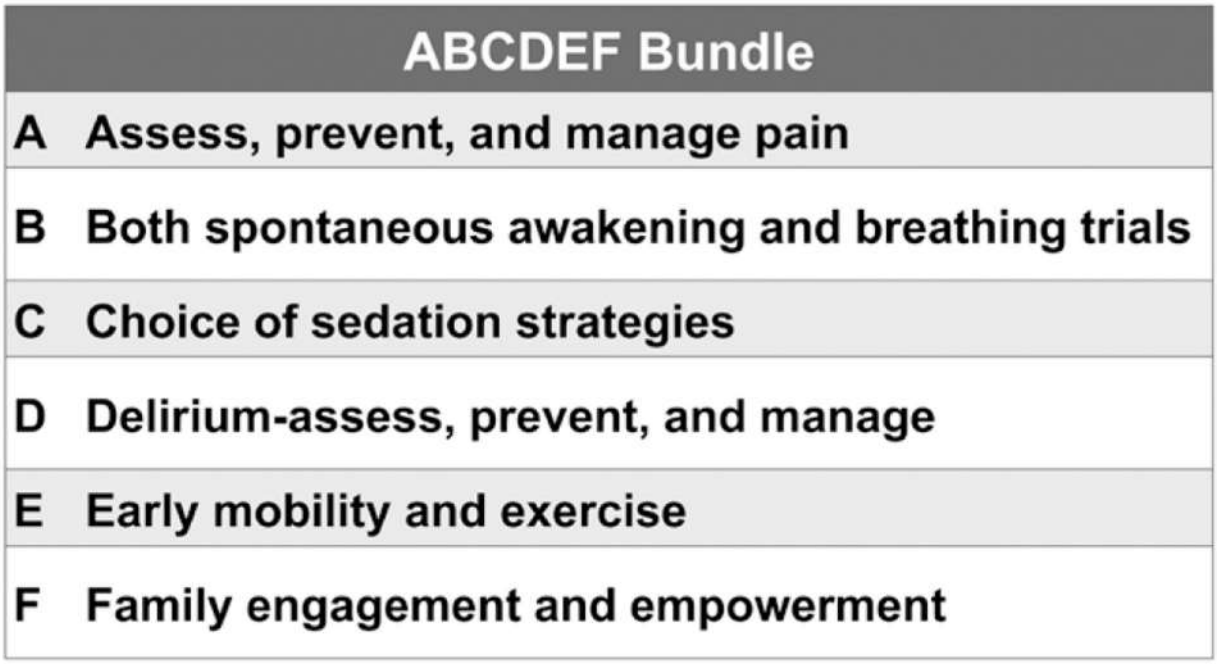

Figure 4.

The ICU liberation (Assess, prevent, and manage pain; Both spontaneous awakening and breathing trials; Choice of Sedation Strategies; Delirium assess, prevent, and manage; Early Mobility and Exercise; Family engagement and empowerment) bundle.

TABLE 1.

Key Attributes of Successful Innovations (14, 31)

Attribute	Definition
Relative advantage	Innovations that have a clear, unambiguous advantage in either their clinical or cost effectiveness
Compatibility	Innovations that are compatible with the intended adopter's values, norms, and perceived needs
Complexity	Innovations that are perceived by key players as simple to use
Trialability	Innovations that intended users can experiment with on a limited basis
Observability	The benefits of an innovation are visible to intended adopters
Reinvention	Innovations that potential adopters can adapt, refine, or otherwise modify to suite their own needs
Fuzzy boundaries	Innovations with a "hard core" and a "soft periphery" that can be adapted to the organization
Risk	Innovations with a low degree of uncertainty of outcome
Task issues	The innovation is relevant to the performance of the intended user's work, and it improves task performance
Knowledge	The knowledge required to use the innovation can easily be codified and transferred from one context to another
Augmentation/support	The technology related to the innovation is supplied with customization, training, and help desk support

TABLE 2.

Variably Adopted Evidence-Based Critical Care Practices That Could Benefit From Implementation Science Methods[a]

Intervention	Trial Result	Practice Recommendation
Gastrointestinal stress ulcer prophylaxis (39, 40)	Lower prevalence of gastrointestinal bleeding and pneumonia in patients receiving proton pump inhibitors or H_2-receptor antagonists	Stress ulcer prophylaxis should be prescribed to critically ill patients at high risk for gastrointestinal bleeding (i.e., MV > 48 hr, coagulopathy, known gastrointestinal ulcer)
Head of bed elevation (41–43)	Reduced rates of VAP with head of bed elevation ≥ 30° in MV patients	In MV patients, elevate head of bed to ≥ 30° as long as it does not pose a risk/conflict with patient care
Restrictive hemoglobin transfusion threshold (≤ 7 g/dL) (44–46)	Restrictive (≤ 7 g/dL) vs liberal (≤ 9 g/dL) hemoglobin strategy associated with fewer blood transfusions, but no difference in mortality	In the absence of specific comorbidities or acute illness-related factors (i.e., active bleeding, ischemia), use a default transfusion threshold of hemoglobin ≤ 7 g/dL (target hemoglobin = 7–9 g/dL)
Low TV ventilation (47)	Reduced mortality in MV patients receiving low TV ventilation	In MV patients with ARDS, target TV = 4–6 mL/kg of PBW; in patients without ARDS, target TV = 6–8 mL/kg PBW
SSS (48–50)	Routine SSS decreases VAP rates, delays VAP onset, shortens duration of MV	Routine SSS is recommended in all MV patients and can lead to improved outcomes, lower VAP rates
PACs (51–53)	No difference in mortality or ICU or hospital LOS in critically ill patients with PAC vs no PAC	In most critically ill patients, PACs are nonbeneficial and potentially harmful, and should not be used regularly
Post-extubation NIV (54–57)	In patients at high risk of extubation failure, post-extubation NIV, vs standard medical therapy or high-flow oxygen via nasal cannula, is associated with lower rates of reintubation, mortality	In patients at high risk for extubation failure (i.e., with preexisting cardiopulmonary disease), preventive NIV should be applied immediately following extubation for ≥ 24 hr
Central venous catheter checklist (58)	Reduction in rate of CLABSIs	Use five-item CLABSI checklist and nursing supervision when inserting central venous catheters
Daily paired SAT + SBT (59–61)	Shorter duration of MV, coma, ICU LOS in patients undergoing paired daily SAT + SBT	Perform “wake up and breathe” protocol daily on MV patients who pass SAT/SBT safety screens
Early rehabilitation and mobilization (62–64)	Early rehabilitation/mobilization (vs usual care) is associated with shorter LOS, duration of delirium, more ventilator-free days, better functional outcomes	Early rehabilitation or mobilization in critically ill patients is feasible, safe and beneficial, and should be performed daily in patients
BG control (65)	Reduced 90-d mortality with conventional (< 180 mg/dL) vs intensive (81–108 mg/dL) BG control	Maintain BG < 180 mg/dL in critically ill patients
PN (66)	Shorter ICU/hospital LOS, duration of MV and renal replacement therapy, and fewer new infections with late vs early PN	In critically ill patients receiving insufficient enteral nutrition, providing supplementary PN early (≤ ICU day 7) vs late (> ICU day 7) is associated with worse outcomes and should be avoided
Gastric residual volume monitoring (67)	No difference in VAP rates, other ICU outcomes with none vs every 6 hr gastric residual volume monitoring	Do not routinely check gastric residual volumes in critically ill patients receiving enteral nutrition
Prone positioning in ARDS (68)	Lower mortality, ventilator-free days in MV patients with severe ARDS undergoing early and prolonged prone vs standard supine positioning	Experienced centers should prone MV patients with severe ARDS early (< 36 hr after intubation) and for ≥ 16 hr each day
Balanced crystalloids for IV fluid replacement (69)	Lower 30 d rate of major adverse renal events (i.e., mortality, new renal replacement therapy, persistent renal dysfunction) in patients receiving balanced crystalloid (i.e., plasmalyte-A or lactated Ringer’s solution) vs normal saline	Compared with balanced crystalloids, routine use of normal saline in critically ill patients may be unsafe and should be avoided

Intervention	Trial Result	Practice Recommendation
Higher PEEP in ARDS (70)	Improved mortality with high vs low PEEP in MV ARDS patients with a positive oxygenation response to higher PEEP	Higher PEEP should be delivered to MV ARDS patients with a positive response to higher PEEP ($\Delta PaO_2/FIO_2 > 0$))
Hour-1 sepsis bundle (71)	Lower mortality and cost in sepsis patients receiving an aggressive resuscitation bundle within 1 hr of identification of severe sepsis or septic shock	Within 1 hr of sepsis identification: 1) measure lactate level; 2) obtain blood cultures; 3) give broad spectrum antibiotics; 4) give 30 mL/kg crystalloid for MAP < 65 or lactate ≥ 4 mmol/L; and 5) give vasopressors for persistent hypotension to keep MAP ≥ 65 mm Hg
ICU liberation (ABCDEF) bundle (72)	Completion of ABCDEF bundle elements is associated with reduced mortality, duration of MV, coma, delirium, and physical restraint use, and lower-skilled nursing facility discharge rates	Complete all elements of the ABCDEF bundle in every critically ill patient every day
Pneumatic compression for DVT prophylaxis (73)	No difference in incidence/prevalence of DVTs in the pneumatic compression group vs control group	Do not use sequential mechanical compression devices in ICU patients already receiving prophylactic anticoagulation

ABCDEF = Assess, prevent, and manage pain; Both spontaneous awakening and breathing trials; Choice of Sedation Strategies; Delirium assess, prevent, and manage; Early Mobility and Exercise; Family engagement and empowerment, ARDS = acute respiratory distress syndrome, BG = blood glucose, CLABSI = central line-associated bloodstream infection, DVT = deep vein thrombosis, LOS = length of stay, MV = mechanically ventilated, NIV = noninvasive ventilation, PAC = pulmonary artery catheter, PBW = predicted body weight, PEEP = positive end-expiratory pressure, PN = parenteral nutrition, SAT = spontaneous awakening trial, SBT = spontaneous breathing trial, SSS = subglottic secretion suctioning, TV = tidal volume, VAP = ventilator-associated pneumonia.

[a]Recommendations chosen are those that are low-cost and supported by multiple and/or single large randomized trials but variably adopted and sustained in real-world ICU settings.