

STUDY PROTOCOL

Open Access



Awareness with paralysis and symptoms of post-traumatic stress disorder among mechanically ventilated emergency department survivors (ED-AWARENESS-2 Trial): study protocol for a pragmatic, multicenter, stepped wedge cluster randomized trial

Brian M. Fuller^{1*}, Brian E. Driver², Michael B. Roberts³, Christa A. Schorr⁴, Kathryn Thompson⁵, Brett Faine⁶, Julianne Yeary⁷, Nicholas M. Mohr⁸, Ryan D. Pappal⁹, Robert J. Stephens¹⁰, Yan Yan¹¹, Nicholas J. Johnson¹² and Brian W. Roberts¹³

Abstract

Background Awareness with paralysis (AWP) is memory recall during neuromuscular blockade (NMB) and can cause significant psychological harm. Decades of effort and rigorous trials have been conducted to prevent AWP in the operating room, where prevalence is 0.1–0.2%. By contrast, AWP in mechanically ventilated emergency department (ED) patients is common, with estimated prevalence of 3.3–7.4% among survivors given NMB. Longer-acting NMB use is a critical risk for AWP, and we have shown an association between ED rocuronium use and increased AWP prevalence. As NMB are given to more than 90% of ED patients during tracheal intubation, this trial provides a platform to test an intervention aimed at reducing AWP. The overall objective is to test the hypothesis that limiting ED rocuronium exposure will significantly reduce the proportion of patients experiencing AWP.

Methods This is a pragmatic, stepped wedge cluster randomized trial conducted in five academic EDs, and will enroll 3090 patients. Per the design, all sites begin in a control phase, under observational conditions. At 6-month intervals, sites sequentially enter a 2-month transition phase, during which we will implement the multifaceted intervention, which will rely on use of nudges and defaults to change clinician decisions regarding ED NMB use. During the intervention phase, succinylcholine will be the default NMB over rocuronium. The primary outcome is AWP, assessed with the modified Brice questionnaire, adjudicated by three independent, blinded experts. The secondary outcome is the proportion of patients developing clinically significant symptoms of post-traumatic stress disorder at 30 and 180 days after hospital discharge. We will also assess for symptoms of depression and anxiety, and health-related quality of life. A generalized linear model, adjusted for time and cluster interactions, will be used to compare AWP in control versus intervention phases, analyzed by intention-to-treat.

*Correspondence:

Brian M. Fuller

fullerb@wustl.edu

Full list of author information is available at the end of the article



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Discussion The ED-AWARENESS-2 Trial will be the first ED-based trial aimed at preventing AWP, a critical threat to patient safety. Results could shape clinical use of NMB in the ED and prevent more than 10,000 annual cases of AWP related to ED care.

Trial registration ClinicalTrials.gov identifier [NCT05534243](https://clinicaltrials.gov/ct2/show/study/NCT05534243). Registered 06, September 2022.

Keywords Emergency medicine, Awareness with paralysis, Sedation, Post-traumatic stress disorder, Mechanical ventilation, Critical care

Background

Awareness with paralysis (AWP) is explicit memory recall during neuromuscular blockade (NMB) [1–3]. It is crippling and can cause catastrophic psychological harm including post-traumatic stress disorder (PTSD), depression, anxiety, complex phobias, and lead to suicide [3–9]. Decades of rigorous investigations on hundreds of thousands of patients have been completed with the goal to prevent AWP in the operating room, where prevalence is approximately 0.1–0.2% [3, 10].

By contrast, comparatively little investigation into AWP has occurred among emergency department (ED) patients, where mechanical ventilation is required for almost 400,000 patients annually in the USA [11]. Important risk factors for AWP identified in operating room patients include (1) use of longer-acting NMB; (2) lack of sedation depth monitoring; (3) total intravenous (versus inhaled) anesthesia; and (4) under dosing of anesthesia [1–3, 10]. Clinical data suggests that ED sedation practices place patients at high risk for AWP (Fig. 1). These practices include a lack of any analgesia and sedation for

20–45% of ED patients after intubation, with up to 33% of patients with no sedation depth assessment while mechanically ventilated in the ED [12, 13]. In addition, approximately 90% of patients are given NMB to facilitate tracheal intubation in the ED, with an increasing use of longer-acting NMB such as rocuronium (versus succinylcholine) [14]. Since these patients cannot move, nor relay pain or fear, they commonly receive lower doses of sedation, and in delayed fashion, with up to 25% receiving sedation after a delay of ≥ 50 min [13–16]. Importantly, high variability exists between sites, as the ED-SED Study demonstrated a wide range of (1) no sedation (site ranges, 5.9–52.6%); (2) post-intubation NMB use (0–27.3%); and (3) sedation monitoring (0–100%) [17]. Similarly, in a secondary analysis of the LOTUS-FRUIT study, 26% of ED patients were given no sedation, and 70% had no sedation depth assessed (site ranges, 0–100%) [18].

The data cited above provided our research group with the preliminary data to justify further study of AWP among mechanically ventilated ED patients. The ED-AWARENESS Study was a single-center, prospective

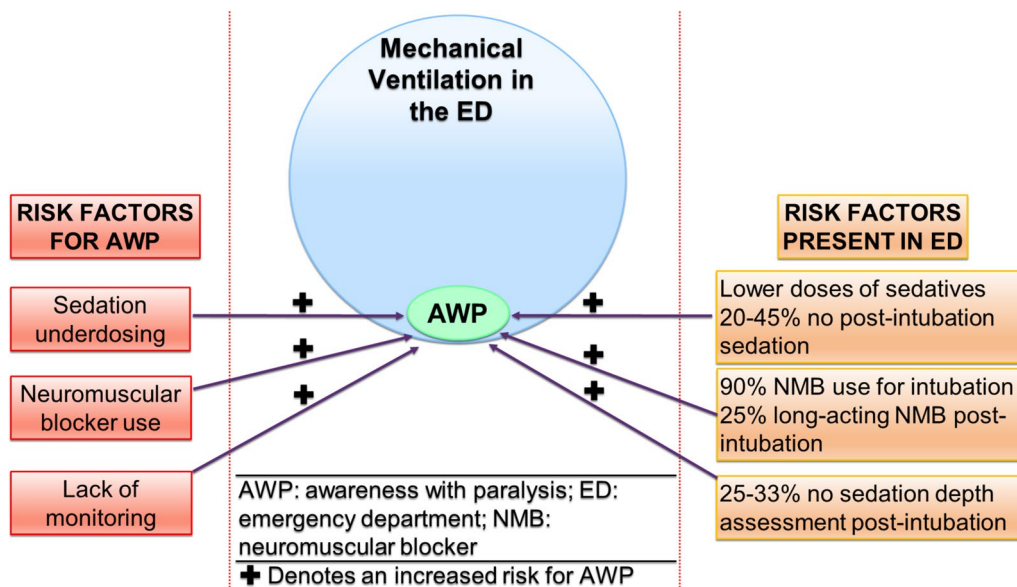


Fig. 1 Important risk factors for awareness with paralysis include sedation under dosing, neuromuscular blocker use, and a lack of protocolled monitoring of sedation depth. Every major risk factor for awareness with paralysis commonly occurs in the emergency department

cohort study which consecutively enrolled 383 mechanically ventilated ED patients over a 12-month period at a large academic medical center [19, 20]. Among survivors given NMB in the ED, the proportion of patients experiencing AWP was 3.3% (10/306; 95% CI, 1.6–5.9%) [19]. In an a priori secondary analysis of the multicenter ED-SED Pilot Trial, we demonstrated that 4.1% (13/314; 95% CI, 2.2–7.0%) of survivors that were given a NMB in the ED experienced AWP [21–23]. Finally, in a single-center prospective cohort conducted at Hennepin County Medical Center (an enrolling site for the current trial), the proportion of patients experiencing an AWP event was 7.4% (66/886; 95% CI, 5.8–9.4%) [24]. Taken as a whole, these data justify a clinical trial aimed at prevention of AWP among mechanically ventilated ED patients and strongly suggest the ED could be a high-yield arena in which to improve patient-centered clinical outcomes.

Psychological trauma and PTSD are a significant burden among the critically ill. PTSD is the development of significant distress or social impairment in someone directly or indirectly exposed to death, threatened death, injury, or violence. Critical illness is psychologically traumatic, and 25–35% of survivors experience PTSD [25–27]. These survivors have worse quality of life, greater frequency of pain and substance abuse, increased health-care cost, and threefold greater risk of death [28–33].

However, similar to AWP, there is a significant knowledge gap with respect to critically ill, mechanically ventilated ED patients. Prior ED-based PTSD work has largely focused on traumatic injury or specifically excluded mechanically ventilated patients [34–37]. In a cohort study of 99 ED patients, our team demonstrated clinically significant PTSD symptoms in 31% of patients with acute respiratory failure, but only 9 patients (9.1%) were mechanically ventilated [38]. Therefore, the burden of PTSD in this cohort is unknown, and the ED could be an optimal target for improving mental health outcomes for several reasons. Critical illness-related mental health disorders are linked to exposures during care, and early frightful memories during illness are linked to higher PTSD prevalence [1, 26]. In addition, delays in care for PTSD are common and linked to refractory symptoms [6, 39–41]. This evidence suggests

the early period of critical illness opens a window to reduce psychological morbidity in survivors. The ED-AWARENESS-2 Trial will inform creation of interventions to be used during (not after) an event to mitigate symptom development, and it will use the ED as a target in which to improve outcomes during the “golden hours” (Fig. 2) [34, 42].

There is significant rationale to target rocuronium use in the ED as a means to prevent AWP. In the ED-AWARENESS Study and ED-SED Pilot Trial, 19/23 (92.6%) AWP patients received rocuronium [19, 23]. In multivariable analysis, rocuronium was independently associated with AWP (adjusted odds ratio, 6.05; 95% CI, 1.46–17.56) [19, 23]. Importantly, AWP was not associated with other sedation-related variables, including (1) sedation monitoring; (2) analgesics, sedatives; or (3) sedation depth. This confirms that a proposal to target ED-based rocuronium may have the greatest chance to improve safety and prevent AWP. This is critical as data from the National Emergency Airway Registry ($n = 17,583$) show rocuronium use was 5% for intubations in 2002, yet up to ~45% by 2012 [14]. Use was up to 49% in our ED SED Study, and 60% in the ED-SED Pilot Trial [17, 21]. This indicates that AWP is likely a growing health problem. Contrary to a 5-min duration of succinylcholine (the historical default NMB), rocuronium can paralyze for up to 150 min, greatly increasing AWP risk. In addition, in clinical trials comparing rocuronium versus succinylcholine, with respect to intubating conditions, data has either favored succinylcholine or shown no difference in outcomes [43–45]. However, other preliminary work from our research team did not show an association between rocuronium and AWP risk, but rather pre-intubation mental status [24]. This suggests equipoise in the data and further confirms the need for this large-scale clinical trial.

Our objective is to conduct a pragmatic clinical trial aimed at limiting rocuronium exposure in order to reduce the proportion of mechanically ventilated ED patients experiencing AWP. We hypothesize that limiting rocuronium exposure in the ED, using succinylcholine as the default NMB of choice, will significantly reduce the proportion of patients experiencing AWP.

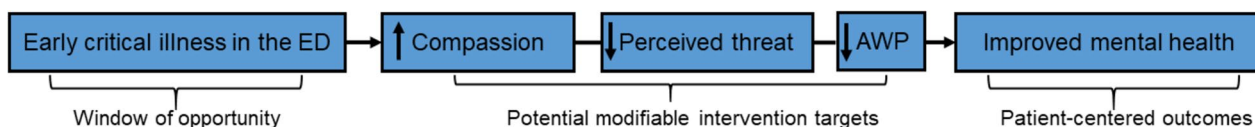


Fig. 2 Example novel paradigm and hypothesized causal pathway for improving patient-centered outcomes. It is possible that by addressing the early period of critical illness in the emergency department, modifiable targets (increasing provider compassion, decreased patient-perceived threat, preventing awareness with paralysis) can be used to improve patient-centered clinical outcomes

Methods

Trial design

This is a multicenter, pragmatic, stepped wedge cluster randomized superiority trial enrolling at five academic sites over an approximately 3.5-year period, divided into six time periods of 6 months each. A schematic of the trial design appears in Fig. 3. Prior to the trial, each site (one site equals one cluster) was randomly allocated to their position within the design. One cluster will cross to the intervention period, at which point succinylcholine will become the default NMB in the ED, every 6 months (i.e., step duration) from the 2nd to the 6th time period. Cluster order will be determined by computer-based randomization, conducted and generated by the trial statistician (YY), and concealed from each site. To begin, each site will be exposed to control conditions; by the end of the trial, each site will be exposed to the intervention. Enrollment began in June of 2023 and we anticipate recruitment of the total sample size to be completed by September of 2026.

A stepped wedge cluster randomized design was chosen for several reasons. It is a robust approach to test quality improvement interventions, such as that in the ED-AWARENESS-2 Trial, and is a rigorous way to study interventions during routine implementation [46, 47]. In addition, randomization of individual patients would be logistically infeasible and yield a small and very selective study population, undermining external validity. Stepped wedge designs are naturalistic because implementation can proceed much as it would without the trial and are

also rigorous because they provide randomized evidence of effectiveness [47]. The design also allows between- and within-group comparisons, enhancing statistical power [47–49]. Finally, a stepped wedge study is ideal when evidence already exists, yet there is suboptimal uptake; based on years of operating room research and our preliminary data, we know an effective way to prevent AWP is to limit use of longer-acting NMB, such as rocuronium [3, 19, 23]. The increase in rocuronium use in the ED over the past several years has occurred without any robust randomized evaluation of patient-centered outcomes, as outcomes have typically centered around intubation success rate [14]. The unintended consequence is an incidence of AWP that threatens patient safety. The stepped wedge design provides a means to conduct the first patient-centered, randomized evaluation on this topic and optimizes enrollment due to potential benefits of the intervention while the trial is ongoing.

Study setting and population

This trial will target mechanically ventilated adult patients in the ED of five academic medical centers. Inclusion criteria are (1) mechanical ventilation via an endotracheal tube; (2) age ≥ 18 years; and (3) treatment with a NMB in the ED (for tracheal intubation or in the post-intubation phase of care). Exclusion criteria are (1) acute or chronic neurologic injury with deficit that prevents assessment of AWP (i.e., stroke, intracranial hemorrhage, traumatic brain injury, cardiac arrest, advanced

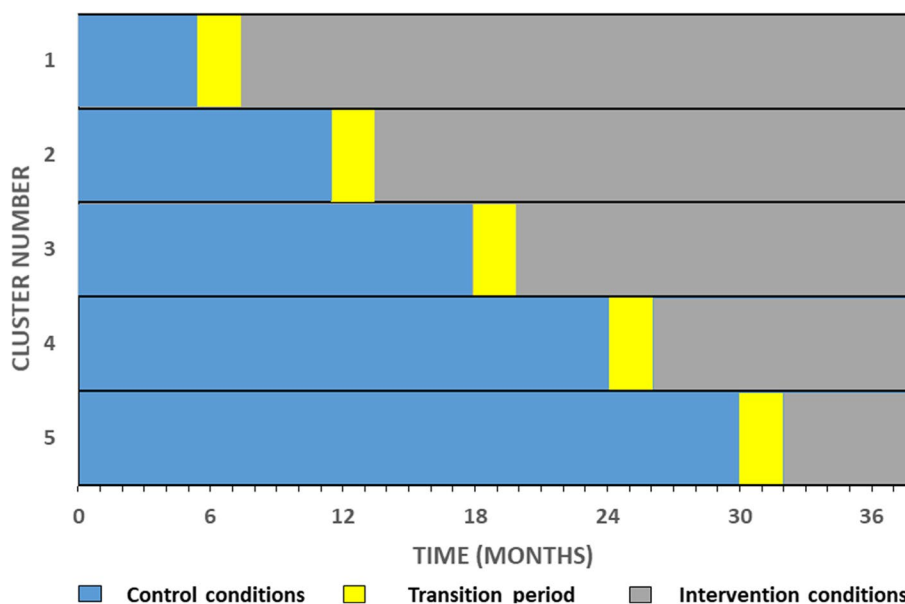


Fig. 3 Stepped wedge cluster randomized trial where clusters cross to intervention every 6 months (step duration), with a preceding 2-month transition to implement the intervention

dementia); (2) death before extubation; and (3) transfer to another hospital from the ED.

Patients will be recruited from the ED at five academic medical centers in the USA: (1) Cooper Medical School of Rowan University, Camden, NJ; (2) University of Iowa, Iowa City, IA; (3) Hennepin County Medical Center, Minneapolis, MN; (4) Barnes-Jewish Hospital/Washington University School of Medicine, St. Louis MO; and (5) Harborview Medical Center, Seattle, WA. Washington University will serve as the Clinical Coordinating Center (CCC) for the trial. The CCC is composed of the overall trial PI, research coordinators, and grants management team, and is responsible for the administration and management of the trial. Mechanically ventilated patients in the ED reflect the composition of the demographics at each of the sites in this study. Based on our preliminary data, we project that the enrollment of women will be approximately 45% and the enrollment of minorities will be approximately 35% Black or African-American, 10% Asian, and 10% Hispanic. We will not exclude any subjects based on gender, race, or ethnicity. We therefore expect that the study findings will hold external validity.

Screening and study initiation

This study will identify those patients who present to the ED and require mechanical ventilation. Each site has a system in place for real-time alerts (24 h/day) when mechanical ventilation is used in the ED, and has validated its notification system from the ED to ensure the population of potentially eligible patients will be consecutive mechanically ventilated patients presenting to the ED. All patients that satisfy inclusion and exclusion criteria will be enrolled.

Interventions

Patients in the control phase of the trial will receive usual, clinician-directed care. To limit a Hawthorne-like effect, clinicians will have no knowledge of the study during the control. After 6 months, as determined by computer-generated randomization, a site will enter a 2-month transition phase, during which we will implement a multifaceted intervention aimed at reducing the use of rocuronium in the ED and consequently increase the use of succinylcholine. The intervention will be delivered at the cluster level, and the strategies employed revolve around the use of “nudges” without restricting clinician choice [50]. Nudges can be a powerful strategy to modify clinician behavior in order to increase uptake of evidence-based practices [48, 50–52]. A type of nudge involves the use of “defaults”; default options are those set in place when no alternatives are actively chosen and they have been shown to positively influence clinician decisions [50]. Succinylcholine will be the default NMB over

rocuronium because (1) it has been the default NMB of choice in the ED for > 40 years [53]; (2) its 5-min duration of action greatly reduces AWP risk; (3) our preliminary data regarding AWP and its association with rocuronium [19, 23]; (4) ED rocuronium use has increased despite no patient-centered studies showing benefit over succinylcholine [17, 21]; and (5) a robust body of literature which documents equivalent efficacy and safety profiles of succinylcholine and rocuronium [54–56].

A basic challenge of pragmatic clinical trials is to design an intervention that is appropriately balanced with respect to flexibility (i.e., it must be adaptable to local culture) and adherence (i.e., it must cause some level of change in order for efficacy to be adequately tested). In addition, a fundamental aspect of nudges is their influence on decisions without restricting choice. Due to these issues, our multifaceted intervention strategy will have both mandatory (standardized) and optional interventions during the transition phase. For the mandatory interventions, we will educate and engage (1) with emergency medicine (EM) physician and nursing leadership to secure endorsement of the trial; and (2) to deliver standardized presentations and lectures to clinicians and trainees (e.g., grand rounds, faculty meetings). We will also use passive alerts in the form of (1) strategically placed laminated graphics which advertise and promote the trial in the ED; and (2) distribution of a one-page document, which contains the background, rationale, and goals of the trial in one convenient location. Finally, active alerts will include (1) announcement of succinylcholine as the default NMB in the nursing “huddle” (before shifts); and (2) monthly emails to clinicians showing the breakdown of NMB use (continuous quality improvement). Optional interventions will be dictated by local culture and resources, or as needed if intervention fidelity declines over time. These include the use of ED-based pharmacy resources to advertise and promote the trial, as well as modification of access to rocuronium, making succinylcholine a more “convenient” option to clinicians (e.g., in the bedside airway box versus the automated medication dispensing system). If needed, we will identify more local champions, in addition to each site principal investigator, to participate in and promote the trial. Finally, if needed we will send emails to individual clinicians each time rocuronium is used in order to explore the rationale for its choice. This provides *accountable justification* regarding NMB choice (i.e., justification of the decision to not use the default). After the 2-month transition phase, each site will begin the intervention phase, in which enrollment will be resumed.

We will aim to prevent drift of intervention fidelity over time in several ways. Sites with an earlier transition to the intervention will be able to advise subsequent sites

on troubleshooting, potential pitfalls, and successes. In addition, the active alerts (see above) will provide routine reminders to the clinical staff regarding the trial. We will also monitor the breakdown of NMB use on a rolling and near-continuous basis and present these results at our ED-AWARENESS-2 team meetings. If problems with treatment fidelity are observed, we will re-educate clinical staff at the site and tailor the intervention re-education as needed. In addition, we will more uniformly employ the optional interventions in order to increase intervention fidelity. In this way, we not only have uniform and mandatory interventions to be employed at the onset of the trial at each site, but also maintain optional interventions which can be strategically “in our back pocket” if needed.

Informed consent

We will conduct the study with waiver of the requirement to obtain signed informed consent. The control phase is entirely observational. The intervention uses nudges and defaults for quality improvement, according to guidelines and recommendations regarding AWP prevention. In addition, for continued monitoring and quality improvement, the assessment of AWP is part of standard routine post-intubation care for millions of mechanically ventilated patients undergoing anesthesia annually in the USA, and it is also part of ongoing quality improvement initiatives in mechanically ventilated ED patients. However, all care will remain at the discretion of treating clinicians, and data during the intervention phase will also be collected under observational conditions. Specifically, while our intervention is aimed at reducing the use of rocuronium in the ED in order to prevent AWP, the final choice of all treatment decisions will remain at the discretion of the treating clinical team at all times. The only processes for research are administration of the mental health and quality of life questionnaires, at days 30 and 180, and medical record review. Verbal informed consent will be obtained prior to administration of the day-30 and day-180 follow-up questionnaires.

Washington University in St. Louis will act as the single institutional review board for this trial. The study protocol has received ethical approval (Additional File 1) by the Human Research Protection Office at Washington University School of Medicine in St. Louis (IRB # 202207132).

Outcome measures

The primary outcome is the proportion of patients experiencing AWP in the control phase versus the intervention phase. Our methodology to assess for AWP is congruent with large operating room trials, and our prior approach [19, 20, 57, 58]. The modified Brice questionnaire has been used for >50 years to assess for AWP and

will be used in this trial (Additional File 2) [59]. To be considered for AWP, patients must report memory of paralysis either before (i.e., recall of intubation) or after (i.e., waking with paralysis) losing consciousness [19]. Because of simplicity and excellent diagnostic accuracy, the Richmond Agitation-Sedation Scale (RASS) will be used to screen for delirium and before assessment of AWP [60]. AWP will be assessed at one time point. Trained team members who will check the medical record daily for extubation and assess for AWP before hospital discharge, under waiver of the requirement to obtain signed informed consent. In patients discharged during off hours (e.g., weekends, night), we will assess AWP via telephone. The final determination of AWP will be independently adjudicated by three experts who will be provided questionnaire responses, qualitative reports of patient experience, and pertinent clinical data. Reviewers will adjudicate events as no, possible, or definite AWP, and determined when \geq two agree. If all hold opposing views, a fourth reviewer will assist. Reviewers will be blinded to NMB, sedation medications, and trial phase.

Secondary outcomes include mental health and quality of life assessments at 30 and 180 days after hospital discharge, assessed via telephone follow-up after obtaining verbal informed consent. Questions will be asked in reference to the index hospitalization. PTSD symptoms will be measured using the PTSD Checklist for DSM-5 (PCL-5), a validated 20-item (score 0–4, Likert scale) self-reported measure that assesses 20 DSM-5 symptoms of PTSD (clinically significant symptoms = PCL-5 > 32) [61]. While PTSD is our main secondary outcome of concern, depression, anxiety, and impaired quality of life (QOL): (1) often co-exist with PTSD; (2) are common after critical illness; and (3) are also sequela linked to AWP [1, 2, 5, 7, 10, 25, 62, 63]. To give a broad picture of burden endured by survivors, we will assess for depression and anxiety with the Hospital Anxiety and Depression Scale (HADS), a validated 14-item (7 depression, 7 anxiety, ordinal score 0–3) questionnaire commonly used in critical illness [25]. We will evaluate QOL with EuroQol-5D (EQ-5D), the most widely used scale for measuring health-related QOL and part of the core sets recommended for critical care studies on post-discharge outcomes [64, 65].

To assess for potentially modifiable intervention targets for future trials aimed at PTSD symptom prevention, we will collect patient perception of (1) perceived threat; (2) clinician compassion; and (3) degree of family/friend emotional support. Perceived threat will be measured with the validated 7-item tool used in our prior work [19, 38, 66, 67]. Patient perception of clinician compassion will be assessed with a 5-item measure,

developed, and validated by our team (only instrument validated for ED use) [68]. Family/friend emotional support during hospitalization will be assessed with two items previously used in the ED as measures of anxiety-provoking social support that are significantly associated with PTSD symptoms: (1) “How much of the time did your support person need you to comfort them?”; and (2) “How much of the time did your support person make you anxious?” [69].

Data

Patient-level data will be easily accessible from the electronic medical record. The following baseline characteristics will be collected: age, gender, race, weight, height, pre-existing comorbid conditions, vital signs at presentation, and pertinent laboratory variables. Pre-intubation mental status, drugs used to facilitate intubation, and ventilator settings in the ED will be collected. After the initiation of mechanical ventilation in the ED, all medications related to analgesia and sedation in the ED will be collected. Sedation depth in the ED will be recorded by bedside nurses, using validated sedation depth scales, such as RASS or the sedation-agitation scale (SAS), per existing protocols [70].

The following in-hospital data will be collected: duration of ventilation, agents used for analgesia and sedation during the first 24 h of ICU admission, depth of sedation during the first 7 days after admission, lengths of stay in the ICU and hospital, discharge location, and mortality status (Table 1).

Data management and quality control

Data will be managed using Research Electronic Data Capture (REDCap), including regulatory document management, data entry and validation, source document and progress monitoring, subject tracking, and secure data transfer [71, 72]. During study initiation, weekly communication will occur with each site via video conference. During these initial meetings, REDCap data fields and entry will be reviewed in detail, tested at each site, and troubleshooting and modification will occur as needed to streamline efficient data entry. Throughout the study, data checks for valid ranges and completeness of data will occur. We will track and identify for each subject the study forms that are expected but not yet entered into REDCap. All site personnel will have ability to run reports that will provide detailed lists of expected forms and of all data queries for their site. In addition, the CCC will provide reports to site investigators, as needed, for timely submission of data forms and resolution of queries. All data will be entered into REDCap by site personnel.

Excluding questionnaires, all data will be obtained from the medical record and verified before data entry. In REDCap, validation rules will ensure acceptable ranges, and valid and accurate data, which will be monitored for errors on an ongoing basis. Any concerns or discrepancies will be resolved by study sites and the CCC; re-training will occur as needed. Routine monthly and ad hoc reports will be run as part of quality control. The reports will track patient accrual and status, data completeness, and responses to data queries.

Data entered into REDCap will be stored on Washington University servers. User privileges related to data management, beyond data entry, will be restricted. As standard operating procedure, use of REDCap to enter and store data, in a secure and password-protected manner, provides certainty that data will not be lost. After study completion, de-identified data will be exported into a statistical analysis package and analyses will proceed in a way such that patient confidentiality is maintained.

Safety monitoring

A data and safety monitoring board (DSMB), independent of the research team and sponsor, will be used to monitor the data. The DSMB will assess safety and efficacy of trial procedures and monitor the overall conduct of the trial. The DSMB also will review adverse event data, other safety data, quality and completeness of data, protocol adherence data, and enrollment data at each meeting to ensure proper trial conduct and continued feasibility of answering the research questions. Meetings between the research team and the DSMB will occur before the study begins, after 25% of the total sample size is accrued each time, and upon trial completion.

The intervention is designed to enhance patient safety by quality improvement related to the selection of neuromuscular blockers by clinicians. Consequently, we aim to see an increase in succinylcholine use during the intervention phase of the trial, which is congruent to clinical practice for more than 40 years and consistent with recommendations for preventing awareness with paralysis. There is over a decade of research on tens of thousands of patients showing equivalent intubation success rates between succinylcholine and rocuronium. In addition, intubation success rate in the ED approaches 100% [14, 54]. We therefore, do not expect to see any difference in intubation success rate between the control and intervention phases, but will track and report this measure. Given the typically small and transient increase in serum potassium of ~0.5 to 1 mEq/L known to occur with succinylcholine, there is the potential for an increase in cardiac arrhythmias related to hyperkalemia to occur in the intervention phase. The overall incidence of cardiac dysrhythmia in the peri-intubation

Table 1 Schedule of screening, data collection, and outcomes assessments for the ED-AWARENESS-2 Trial

Measurement/event	ED	Extubation	^a 1	2	3	4	5	6	7	MV ^b	HOSP D/C	Day 30	Day 180
Inclusion criteria	X												
Exclusion criteria		X											
Demographics, baseline data	X												
Laboratory values	X												
Blood gas values	X		X										
ED procedures and care	X												
Intubation meds and location	X												
Safety events (i.e., intubation success, unplanned extubation, cardiac arrhythmia, allergy, MH)	X												
Ventilator settings/data	X												
Sedation depth (RASS, SAS), documented by bedside nurse	X		X	X	X	X	X	X	X				
Medications for sedation, analgesia, NMB	X		X										
Delirium assessment/CAM-ICU			X	X	X	X	X	X	X				
Assessment of AWP		X											
Ventilator duration										X			
Length of stay (hospital and ICU)											X		
Discharge location											X		
Mortality status											X		
Mental health and QOL assessments												X	X

ED emergency department; MV mechanical ventilation; MH malignant hyperthermia; RASS Richmond Agitation-Sedation Scale; SAS Sedation-Agitation Scale; SAS Sedation-Agitation Scale; MMB neuromuscular blockade; CAM confusion assessment method; ICU intensive care unit; QOL quality of life

^aThe numbers 1–7 refer to hospital days, with hospital day 1 referring to the first day after admission from the ED

^bIf patient is extubated for 24 h or more, then that is the end of ventilation duration. If patient is extubated and re-intubated within 24 h, this is treated as though they were never extubated

period in the ED is approximately 0.7% with no difference between succinylcholine and rocuronium. We therefore do not expect to see any difference in this adverse event between the control and intervention phases, but will track and report this measure [14]. Other very rare adverse events associated with succinylcholine include malignant hyperthermia (incidence ~0.009%) and allergic reaction to succinylcholine (incidence 0.01%) [73, 74]. Both of these adverse events are quite unlikely to occur, but will be tracked and reported. Unexpected events will be reported by the site principle investigators to the CCC as detected.

Adverse events and serious adverse events will be presented at each DSMB meeting. Adverse events will be classified according to severity, relatedness, and expectedness. Each site principle investigator will designate their first impression of the seriousness and relatedness of the adverse events, and this will be forwarded to a centralized independent safety monitor, who will adjudicate final relatedness, seriousness, and expectedness. As the control phase is entirely observational, this review process will pertain to sites after their transition to the intervention phase of the trial. Events will be reported in trial publications.

As the adverse events related to the choice of a particular neuromuscular blocker are so rare, and most adverse events will be related to critical illness itself, we have not established formal stopping rules. Recommendations by the DSMB will be made based on the assessment of clinical outcomes, adverse events, and human subjects risk in totality.

Proposed statistical methods

Patient characteristics will be reported using descriptive statistics and frequency distributions. Continuous variables will be compared using independent samples *t*-test or Mann–Whitney *U* test, and categorical variables will be compared using chi-square test or Fisher's exact test.

AWP will be calculated as proportion (with 95% confidence intervals [CI]) of patients with possible or definite events, as done before [19, 20, 57]. Adjudicator agreement will be assessed, per prior approach, with two-way, random effects, intraclass correlation coefficient for absolute agreement according to 0=no awareness, 1=possible awareness, and 2=definite awareness. All analyses will be intention to treat, such that all patients will be evaluated, regardless of clinician adherence during the intervention phase. The unit of randomization will be the ED, and the unit of analysis will be the patient. The primary analysis will compare the proportion of patients with AWP in the control phase versus the intervention phase. To estimate the intervention effect, mixed effects models and generalized estimating equations (GEE) are

most commonly used in stepped wedge designs. However, due to the smaller number of clusters ($n=5$), it is more appropriate to use a generalized linear model, with cluster included as a fixed effect (i.e., a logistic regression model for binary outcome data with each of five sites as fixed effect) [75–78]. We will first fit a basic model, in which the intervention effect is estimated, adjusting for secular trends (i.e., time effect). We will then extend the basic model by incorporating and testing appropriate interaction terms to test the nature of the intervention effect. Examples include (1) an intervention-by-cluster interaction for heterogeneity of the intervention effect across clusters; and (2) an intervention-by-time for heterogeneity of the intervention effect across time. A possible delayed intervention effect will be tested by changing the intervention indicator (i.e., 0 or 1) into some fractions between 0 and 1, aligned with the time from switching from control to intervention. Unadjusted analyses will also be reported.

Instrumental variable (IV) methods will be used to account for non-adherence, as there could be differences between intervention effectiveness (i.e., effect among all patients to whom the intervention is targeted) and efficacy (i.e., effects among patients whose clinicians adhere to the intervention). We will use a non-parametric IV estimator adapted to stepped wedge designs, and IV regression methods to estimate complier average causal effect (CACE) of the intervention [79]. To avoid conflating the effect of time with the intervention effect, we will (1) obtain step-specific CACE estimates and (2) summarize step-specific estimates across all steps. We will also use two-stage residual inclusion to perform IV regression, using individual data from all six time points, adjusting for time and cluster effects [80–82]. Unlike per-protocol analyses, CACE analyses are not biased by selection effects and have been shown to be valid inferential approaches in stepped wedge trials [79].

We will determine proportion (with 95% CIs) of patients with clinically significant PTSD symptoms (PCL-5 score > 32) at 30 days and 180 days post-discharge [83, 84] and compare the control versus the intervention phase. To test the independent association of AWP (main exposure of interest) with 30-day PTSD symptom development, multivariable logistic regression will be used, with covariates selected for inclusion a priori [85]. The model will be adjusted for covariates previously associated with PTSD symptoms in critical illness survivors: (1) age; (2) sex; (3) prior psychological trauma (PC-PTSD-5 score)/mental health history; (4) illness severity; and (5) receipt and dose of benzodiazepines [10, 25, 26, 62, 86, 87]. We will adjust for race, given known racial disparities in PTSD symptoms [88–91]. To examine time trends in PTSD symptoms, and independent effects of AWP on

time trends, mixed effect logistic regression will be used. Individual random intercept and random time slope will be specified and tested along with other potential risk factors. We will identify individual-level potential risk factors which could explain variation in individual time trend by testing interaction between random time slope and risk factor(s). In all of these models, cluster effect will be modeled as a fixed effect, using cluster indicator in the model. Similar analyses will be conducted for the other secondary outcomes.

Using structural equation modeling, we will test if patient-perceived threat mediates the relationship (i.e., on the causal pathway) between patient perception of clinician compassion and PTSD symptoms (PCL-5 as a continuous variable) at 30 days. To test for mediation, we will calculate the direct effect of patient perception of compassion on PTSD symptoms, as well as the indirect effect of patient perception of compassion on PTSD symptoms that passes through patient-perceived threat, using bootstrapped standard errors and 95% confidence intervals (Fig. 4) [92, 93]. We will perform separate analyses to also test associations between family/friend emotional support [adjusting for support persons physically present (yes/no)] with perceived threat and PTSD symptoms.

Sample size justification

Our sample size is designed to detect a difference in the proportion of patients experiencing AWP in the control versus the intervention phase. The sample size must be inflated by estimating the design effect, to account for the intraclass correlation coefficient (ICC). More common outcomes are associated with higher design effects, whereas lower prevalence outcomes, such as AWP, have smaller ICCs [94]. Based on our data, and extensive supporting analyses from more than 100 ICC values obtained from research studies and population health outcomes analyses ($n > 1,000,000$ patients) which show a strong linear association between the ICC and outcome prevalence in clustered binary data, we conservatively estimate an ICC of 0.001 [94]. From our preliminary multicenter data, due to a reduction in rocuronium use, it is reasonable to estimate a reduction in the proportion of patients

experiencing AWP from 4.0% in the control phase to 0.2% in the intervention phase (data from the operating room), which would require a total sample size of 1650 patients [95]. To err on the side of conservative assumptions, and to account for possible non-adherence during the study, we will assume a prevalence of AWP of 3.3% in the control phase and 0.6% in the intervention phase. These conservative estimates are based on our prior work (control phase), and the intervention phase event rate is similar to that seen in operating room patients managed with total intravenous anesthesia and when longer-acting NMB is limited [10, 19, 96]. Thus, these calculations are both clinically important (would prevent ~10,000 AWP cases annually in the USA) and plausible from supporting preliminary work. Considering there are 5 sites and 6 time periods, for 80% power with α of 0.05, we will need a total sample size 3090 patients.

With respect to PTSD, if we estimate that PTSD occurs in 45% of those with AWP [5, 6, 9] and 20% of the rest of the cohort [25–27], assuming $\alpha = 0.05$ and power = 0.80, using two-sided Z-test with pooled variance, a sample size of 1192 patients will be required for the multivariable model above. With respect to perceived threat, even if correlation between perceived threat and PTSD symptoms is smaller than our prior work (0.3) then a minimum of 412 patients is estimated to detect the mediated effect of perceived threat between clinician compassion and PTSD symptoms [38, 97, 98].

Recruitment

The first patient was recruited on June 29, 2023. Our timeline is based on estimates and prior work conducted previously at our enrolling sites [17–19, 21, 99–101]. Between 750 and 1500 patients need mechanical ventilation in the ED at our sites annually. If we conservatively estimate enrollment of 0.5 patients per day at each site at a minimum, with five sites, enrollment will take ~3.3 years.

Dissemination and data sharing

The ED-AWARENESS-2 Trial is registered on Clinical-Trials.gov (NCT05534243). We will follow current data

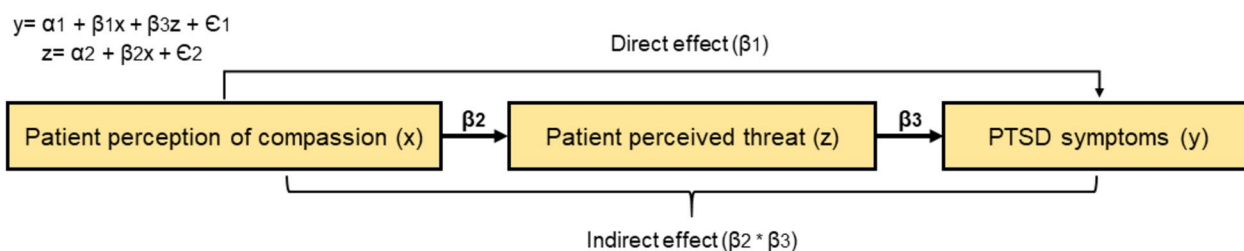


Fig. 4 Structural equation model of the direct and indirect effects of perception of compassion on PTSD symptoms

sharing policies of the funding agency in order to share data with other investigators through academically established means. We designed this study in close adherence to the Pragmatic-Explanatory Continuum Indicator Summary-2 (PRECIS-2) criteria for pragmatic trials, and the Consolidated Standards of Reporting Trials (CONSORT) extension for stepped wedge cluster randomized trials [102, 103]. This protocol manuscript also adheres to the SPIRIT reporting guidelines (Additional File 3 (SPIRIT Checklist) and Fig. 5 (SPIRIT Figure)). The protocol and final results will be published in peer-reviewed journals. Data will be presented at annual critical care and EM conferences. At the current time, there are no formal plans for additional studies using these data.

Discussion

The overall objective of this proposal is to conduct a pragmatic, stepped wedge cluster randomized trial in five academic EDs and to further understand to what extent NMB selection is associated with AWP, our primary outcome. The central hypothesis is that by using nudges and defaults aimed at reducing ED rocuronium use, the proportion of patients experiencing AWP will be significantly reduced. In addition, we hypothesize that the psychological burden suffered by mechanically ventilated ED patients is high, and modifiable targets can be identified. The scientific literature and our preliminary data provide the rationale for conducting this study, and through completion of its aims, we hope to prevent an important threat to patient safety, and develop interventions to be tested in future trials in effort to improve mental health

outcomes in survivors going forward. The public health impact from this proposal resides in the fact that it can be readily implemented broadly to prevent thousands of cases of AWP annually. In addition, by targeting the ED and examining psychological outcomes through a patient-centered lens, our results are expected to have a positive public health impact by elucidating the principal pathways of long-term psychological sequelae of critical illness and clarifying the role of time-sensitive ED interventions in contributing to those outcomes. This will allow us to develop specific, targeted countermeasures to improve long-term outcomes for critical illness survivors and identify promising prevention strategies for ED implementation.

This trial has vital strengths. The design and pragmatic nature reflect real-world settings, generating data: (1) with high external validity; (2) with immediate potential for impact; and (3) that are easily disseminated. The analyses are robust and the outcomes (1) are important to patients, clinicians, policy makers, and society; and (2) provide invaluable patient-centered data in patients with acute respiratory failure. As such, findings could change practice by providing: (1) important patient-centered outcome data regarding ED-based NMB use and (2) evidence to target the ED with patient-centered interventions to mitigate mental health morbidity and inequities going forward. The trial will also enroll the largest critically ill cohort to date for the study of AWP.

Relevant limitations exist. A fundamental challenge of pragmatic trials is designing a flexible yet effective intervention-adherence plan to enhance fidelity. To address

	STUDY PERIODS								CLOSE OUT
	Site Selection	Site Allocation	Control	Intervention Implementation					
TIMEPOINTS	Pre-trial	initiation	Step 0	Step 1	Step 2	Step 3	Step 4	Step 5	
Screening of EDs for eligibility	X								
Allocation of ED position in the trial		X							
Screening patients for inclusion									
Patient enrollment									
INTERVENTION									
Leadership engagement									
Education									
Passive alerts									
Active alerts									
ASSESSMENTS									
Demographic data									
Laboratory data									
ED and ICU sedation-related data									
Clinical outcomes									
Trial-related outcomes									
•AWP									
•Day 30, 180 mental health and QOL									
DATA ANALYSIS									X

ED: emergency department; ICU: intensive care unit; AWP: awareness with paralysis; QOL: quality of life

Fig. 5 SPIRIT flow diagram for the ED-AWARENESS-2 Trial, a stepped wedge cluster randomized trial

this, we will employ a systematic and multifaceted intervention approach, similar to our prior pragmatic work that has been successful in ED-based studies. We will perform secondary efficacy (CACE) analyses among patients who would have received the intervention if assigned to it. The modest frequency of AWP may raise questions regarding the number of patients who may benefit. However, as AWP is so consequential to patients experiencing it, our results are expected to carry significant impact. Further, the entire cohort is at high risk to experience psychological morbidity. By rigorously assessing these outcomes in all patients, we will acquire new knowledge that could benefit all mechanically ventilated patients. The trial design includes follow-up beyond the index hospitalization, and incomplete follow-up is a potential problem. We acknowledge loss to follow-up rates ranging from 16 to 50% in prior critical illness-associated PTSD literature [62, 104]. With a response rate of approximately 40%, the sample size will still be large enough to achieve our aims. We will promote patient retention by making the patients aware of the follow-up calls at day 30, obtaining multiple contact numbers by which to reach them, and by messaging the patients to arrange the most appropriate day and time to call.

Trial status

The current protocol is version 1.0 dated August 9, 2022. The trial initiated enrollment on June 29, 2023, and is expected to be completed in September of 2026.

Abbreviations

AWP	Awareness with paralysis
CACE	Complier average causal effect
CCC	Clinical coordinating center
CI	Confidence interval
CONSORT	Consolidated standards of reporting trials
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSMB	Data and safety monitoring board
ED	Emergency department
EM	Emergency medicine
GEE	Generalized estimating equations
HADS	Hospital anxiety and depression scale
IA	Iowa
ICC	Intraclass correlation coefficient
ICU	Intensive care unit
IRB	Institutional Review Board
IV	Instrumental variable
MN	Minnesota
MO	Missouri
NJ	New Jersey
NMB	Neuromuscular blockade
PC	Primary care
PCL-5	PTSD checklist for DSM-5
PRECIS	Pragmatic-explanatory continuum indicator summary
PTSD	Post-traumatic stress disorder
QOL	Quality of life
RASS	Richmond Agitation-Sedation Scale
REDCap	Research Electronic Data Capture
SAS	Sedation-Agitation Scale
SED	Sedation

WA Washington

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13063-023-07764-5>.

Additional file 1.

Additional file 2. Awareness with Paralysis (AWP) Questionnaire.

Additional file 3. SPIRIT Checklist for *Trials*.

Additional file 4. World Health Organization Trial Registration Data Set items.

Acknowledgements

Not applicable.

Authors' contributions

BMF wrote the first draft of the manuscript. BMF led the protocol development, supported by BWR, BF, NMM, YY, NJJ, and BED. The study design was conceptualized by BMF, BWR, YY, and NMM, and supported by all other authors. YY worked on the statistical details of the trial, supported by BMF, BWR, and NMM. BMF, BWR, BF, NMM, RDP, RJS, YY, NJJ, KT, and BED worked on data management aspects of the protocol, as well as data collection and quality control. The intervention implementation was worked on by BMF, BWR, MR, CS, BF, JY, NMM, RDP, RJS, NJJ, KT, and BED. The assessments of mental health, quality of life, and patient experiences were worked on by MR, BMF, and BWR. The preliminary data to support the trial was obtained by BMF, BWR, MR, BF, NMM, RDP, RJS, YY, NJJ, KT, and BED. All authors played a role in revising the manuscript, subsequent drafting, and have read and given final approval of the final submitted manuscript. Authorship eligibility is determined based on the International Committee of Medical Journal Editors.

Funding

This trial is funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award number R01HL162721. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Funders played no role in the following features of the study: study design, data collection, data management, data analysis, data interpretation, writing of the manuscript, or decision to submit the manuscript for publication.

Availability of data and materials

We will follow current data sharing policies of the funding agency (National Heart, Lung and Blood Institute) in order to share data with other investigators through academically established means.

Declarations

Ethics approval and consent to participate

Washington University in St. Louis will act as the single institutional review board for this trial. The study protocol has received ethical approval by the Human Research Protection Office at Washington University School of Medicine in St. Louis (IRB # 202207132). We will conduct the study with waiver of the requirement to obtain signed informed consent. Verbal informed consent will be obtained prior to administration of the day-30 and day-180 follow-up questionnaires.

Consent for publication

Not applicable as this manuscript does not contain study participant data.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Anesthesiology, Division of Critical Care, Department of Emergency Medicine, Washington University in St. Louis School of Medicine, St. Louis, MO 63110, USA. ²Department of Emergency Medicine, Hennepin

County Medical Center, 701 Park Avenue, Minneapolis, MN 55415, USA.

³Department of Institutional Research, Department of Psychology, Philadelphia College of Osteopathic Medicine, Rowland Hall, 514B, 4190 City Avenue, Philadelphia, PA 19131, USA. ⁴Cooper Research Institute, Cooper University Health Care, One Cooper Plaza, Dorrance, Camden, NJ 08103, USA. ⁵Department of Emergency Medicine, University of Washington/Harborview Medical Center, 325 9th Avenue, Seattle, WA 98104, USA. ⁶Departments of Emergency Medicine and Pharmacy, Roy J. and Lucille A. Carver College of Medicine, University of Iowa College of Pharmacy, 200 Hawkins Drive, 1008 RCP, Iowa City, IA 52242, USA. ⁷Emergency Department, Charles F. Knight Emergency and Trauma Center, Barnes-Jewish Hospital, 1 Barnes Jewish Hospital Plaza, St. Louis, MO 63110, USA. ⁸Departments of Emergency Medicine and Anesthesiology, Division of Critical Care, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, 200 Hawkins Drive, 1008 RCP, Iowa City, IA 52242, USA. ⁹Department of Emergency Medicine, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215, USA. ¹⁰Department of Medicine, Division of Critical Care Medicine, University of Maryland School of Medicine, 655 W. Baltimore Street, Baltimore, MD 21201, USA. ¹¹Division of Public Health Sciences, Department of Surgery, Division of Biostatistics, Washington University School of Medicine, 418E, 2Nd Floor, 600 South Taylor Ave., St. Louis, MO 63110, USA. ¹²Departments of Emergency Medicine and Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, University of Washington/Harborview Medical Center, 325 9th Avenue, Seattle, WA 98104, USA. ¹³Department of Emergency Medicine, Cooper Medical School of Rowan University, One Cooper Plaza, K152, Camden, NJ 08103, USA.

Received: 21 September 2023 Accepted: 30 October 2023

Published online: 25 November 2023

References

- Cook T, Andrade J, Bogod D, Hitchman J, Jonker W, Lucas N, et al. 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: patient experiences, human factors, sedation, consent, and medicolegal issues. *Br J Anaesth*. 2014;113(4):560–74.
- Ghoneim MM, Block RI, Haffarnan M, Mathews MJ. Awareness during anesthesia: risk factors, causes and sequelae: a review of reported cases in the literature. *Anesth Analg*. 2009;108(2):527–35.
- Mashour G, Avidan M. Intraoperative awareness: controversies and non-controversies. *Br J Anaesth*. 2015;115(suppl_1):i20–6.
- Field PR, Gangemi G, Kinsley T. Under the Knife and Completely Aware: A Case of Intraoperative Awareness. NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE. 2013.
- Lennmarken C, Bildfors K, Enlund G, Samuelsson P, Sandin R. Victims of awareness. *Acta Anaesthesiol Scand*. 2002;46(3):229–31.
- Leslie K, Chan MT, Myles PS, Forbes A, McCulloch TJ. Posttraumatic stress disorder in aware patients from the B-aware trial. *Anesth Analg*. 2010;110(3):823–8.
- Samuelsson P, Brudin L, Sandin RH. Late psychological symptoms after awareness among consecutively included surgical patients. *Anesthesiology*. 2007;106(1):26–32.
- Schwender D, Kunze-Kronawitter H, Dietrich P, Klasing S, Forst H, Madler C. Conscious awareness during general anaesthesia: patients' perceptions, emotions, cognition and reactions. *Br J Anaesth*. 1998;80(2):133–9.
- Whitlock EL, Rodebaugh TL, Hassett AL, Shanks AM, Kolarik E, Houghtby J, et al. Psychological sequelae of surgery in a prospective cohort of patients from three intraoperative awareness prevention trials. *Anesth Analg*. 2015;120(1):87.
- Avidan MS, Mashour GA. Prevention of Intraoperative Awareness with Explicit Recall Making Sense of the Evidence. *J Am Soc Anesth*. 2013;118(2):449–56.
- Cairns C, Kang K. National Hospital Ambulatory Medical Care Survey: 2019 Emergency Department Summary Tables. 2022.
- Bonomo JB, Butler AS, Lindsell CJ, Venkat A. Inadequate provision of postintubation anxiolysis and analgesia in the ED. *Am J Emerg Med*. 2008;26(4):469–72.
- Stephens RJ, Ablordeppey E, Drewry AM, Palmer C, Wessman BT, Mohr NM, et al. Analgosedation practices and the impact of sedation depth on clinical outcomes among patients requiring mechanical ventilation in the ED: a cohort study. *Chest*. 2017;152(5):963–71 (PMCID: **PMC5812748**).
- Brown CA, Bair AE, Pallin DJ, Walls RM, Investigators NI. Techniques, success, and adverse events of emergency department adult intubations. *Annals of Emergency Medicine*. 2015;65(4):363–70 e1.
- Korinek JD, Thomas RM, Goddard LA, St John AE, Sakles JC, Patanwala AE. Comparison of rocuronium and succinylcholine on postintubation sedative and analgesic dosing in the emergency department. *Eur J Emerg Med*. 2014;21(3):206–11.
- Weingart GS, Carlson JN, Callaway CW, Frank R, Wang HE. Estimates of sedation in patients undergoing endotracheal intubation in US EDs. *Am J Emerg Med*. 2013;31(1):222–6.
- Fuller BM, Roberts BW, Mohr NM, Knight WA IV, Adeoye O, Pappal RD, et al. The ED-SED Study: A Multicenter, Prospective Cohort Study of Practice Patterns and Clinical Outcomes Associated With Emergency Department SEDation for Mechanically Ventilated Patients. *Crit Care Med*. 2019;47(11):1539–48.
- Steel TL, Lokhandwala S, Caldwell ES, Johnson NJ, Miller CD, Gong MN, et al. Variability in Sedation Assessment among Intubated Patients in the Emergency Department. *Academic Emergency Medicine*. 2021;<https://doi.org/10.1111/acem.14259>.
- Pappal RD, Roberts BW, Mohr NM, Ablordeppey E, Wessman BT, Drewry AM, et al. The ED-AWARENESS Study: A Prospective, Observational Cohort Study of Awareness With Paralysis in Mechanically Ventilated Patients Admitted From the Emergency Department. *Ann Emerg Med*. 2021;77(5):532–44.
- Pappal RD, Roberts BW, Mohr NM, Ablordeppey E, Wessman BT, Drewry AM, et al. Protocol for a prospective, observational cohort study of awareness in mechanically ventilated patients admitted from the emergency department: the ED-AWARENESS Study. *BMJ Open*. 2019;9(10):e033379.
- Fuller BM, Roberts BW, Mohr NM, Faine B, Drewry AM, Wessman BT, et al. The Feasibility of Implementing Targeted SEDation in Mechanically Ventilated Emergency Department Patients: The ED-SED Pilot Trial. *Crit Care Med*. 2022;50(8):1224–35.
- Fuller BM, Roberts BW, Mohr NM, Pappal RD, Stephens RJ, Yan Y, et al. A study protocol for a multicentre, prospective, before-and-after trial evaluating the feasibility of implementing targeted SEDation after initiation of mechanical ventilation in the emergency department (The ED-SED Pilot Trial). *BMJ Open*. 2020;10(12):e041987.
- Fuller BM, Pappal RD, Mohr NM, Roberts BW, Faine B, Yearly J, et al. Awareness with paralysis among critically ill emergency department patients: a prospective cohort study. *Crit Care Med*. 2022;50(10):1449.
- Driver BE, Prekker ME, Wagner E, Cole JB, Puskarich MA, Stang J, et al. Recall of Awareness During Paralysis Among ED Patients Undergoing Tracheal Intubation. *Chest*. 2023;163(2):313–23.
- Hatch R, Young D, Barber V, Griffiths J, Harrison DA, Watkinson P. Anxiety, Depression and Post Traumatic Stress Disorder after critical illness: a UK-wide prospective cohort study. *Crit Care*. 2018;22(1):310.
- Parker AM, Sricharoenchai T, Rapaola S, Schneck KW, Bienvenu OJ, Needham DM. Posttraumatic stress disorder in critical illness survivors: a metaanalysis. *Crit Care Med*. 2015;43(5):1121–9.
- Wade D, Hardy R, Howell D, Mythen M. Identifying clinical and acute psychological risk factors for PTSD after critical care: a systematic review. *Minerva Anesthesiol*. 2013;79(8):944–63.
- Otis JD, Keane TM, Kerns RD. An examination of the relationship between chronic pain and post-traumatic stress disorder. *J Rehabil Res Dev*. 2003;40(5):397–406.
- Pacella ML, Hruska B, Delahanty DL. The physical health consequences of PTSD and PTSD symptoms: a meta-analytic review. *J Anxiety Disord*. 2013;27(1):33–46.
- Roberts AL, Kubzansky LD, Chibnik LB, Rimm EB, Koenen KC. Association of posttraumatic stress and depressive symptoms with mortality in women. *JAMA Netw Open*. 2020;3(12):e2027935.
- Schäfer I, Najavits LM. Clinical challenges in the treatment of patients with posttraumatic stress disorder and substance abuse. *Curr Opin Psychiatry*. 2007;20(6):614–8.
- Stewart SH. Alcohol abuse in individuals exposed to trauma: a critical review. *Psychol Bull*. 1996;120(1):83.

33. Walker EA, Katon W, Russo J, Ciechanowski P, Newman E, Wagner AW. Health care costs associated with posttraumatic stress disorder symptoms in women. *Arch Gen Psychiatry*. 2003;60(4):369–74.
34. Schultebraucks K, Shalev AY, Michopoulos V, Grudzen CR, Shin S-M, Stevens JS, et al. A validated predictive algorithm of post-traumatic stress course following emergency department admission after a traumatic stressor. *Nat Med*. 2020;26(7):1084–8.
35. Bryant RA, O'donnell ML, Creamer M, McFarlane AC, Clark CR, Silove D. The psychiatric sequelae of traumatic injury. *Am J Psychiatr*. 2010;167(3):312–20.
36. Jaramillo S, Suffoletto B, Callaway C, Pacella-LaBarbara M. Early screening for posttraumatic stress disorder and depression among injured emergency department patients: a feasibility study. *Acad Emerg Med*. 2019;26(11):1232–44.
37. Shih RA, Schell TL, Hambarsoomian K, Marshall GN, Belzberg H. Prevalence of PTSD and major depression following trauma-center hospitalization. *J Trauma*. 2010;69(6):1560.
38. Moss J, Roberts MB, Shea L, Jones CW, Kilgannon H, Edmondson DE, et al. Association between perceived threat and the development of posttraumatic stress disorder symptoms in patients with life-threatening medical emergencies. *Acad Emerg Med*. 2020;27(2):109–16.
39. Fikretoglu D, Liu A, Pedlar D, Brunet A. Patterns and predictors of treatment delay for mental disorders in a nationally representative, active Canadian military sample. *Medical Care*. 2010;48:10–7.
40. Maguen S, Madden E, Neylan TC, Cohen BE, Bertenthal D, Seal KH. Timing of mental health treatment and PTSD symptom improvement among Iraq and Afghanistan veterans. *Psychiatr Serv*. 2014;65(12):1414–9.
41. Wang PS, Berglund P, Olfson M, Pincus HA, Wells KB, Kessler RC. Failure and delay in initial treatment contact after first onset of mental disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):603–13.
42. Vermetten E, Zhohar J, Krugers HJ. Pharmacotherapy in the aftermath of trauma; opportunities in the 'golden hours.' *Curr Psychiatry Rep*. 2014;16(7):455.
43. Marsch SC, Steiner L, Bucher E, Pargger H, Schumann M, Aebi T, et al. Succinylcholine versus rocuronium for rapid sequence intubation in intensive care: a prospective, randomized controlled trial. *Crit Care*. 2011;15(4):1–9.
44. Guihard B, Chollet-Xémard C, Lakhnati P, Vivien B, Broche C, Savary D, et al. Effect of rocuronium vs succinylcholine on endotracheal intubation success rate among patients undergoing out-of-hospital rapid sequence intubation: a randomized clinical trial. *JAMA*. 2019;322(23):2303–12.
45. Tran DT, Newton EK, Mount VA, Lee JS, Wells GA, Perry JJ. Rocuronium versus succinylcholine for rapid sequence induction intubation. *Cochrane database of systematic Reviews*. 2015;10:CD002788.
46. Gong M, Schenk L, Gajic O, Mirhaji P, Sloan J, Dong Y, et al. Early intervention of patients at risk for acute respiratory failure and prolonged mechanical ventilation with a checklist aimed at the prevention of organ failure: protocol for a pragmatic stepped-wedged cluster trial of PROOFCheck. *BMJ Open*. 2016;6(6):e011347.
47. Hemming K, Haines T, Chilton P, Girling A, Lilford R. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. *BMJ*. 2015;350:h391.
48. Courtright KR, Dress EM, Singh J, Bayes BA, Chowdhury M, Small DS, et al. Prognosticating Outcomes and Nudging Decisions with Electronic Records in the Intensive Care Unit Trial Protocol. *Ann Am Thorac Soc*. 2021;18(2):336–46.
49. Wortmann JH, Jordan AH, Weathers FW, Resick PA, Dondanville KA, Hall-Clark B, et al. Psychometric analysis of the PTSD Checklist-5 (PCL-5) among treatment-seeking military service members. *Psychol Assess*. 2016;28(11):1392.
50. Halpern SD. Using default options and other nudges to improve critical care. *Crit Care Med*. 2018;46(3):460.
51. Last BS, Bутtenheim AM, Timon CE, Mitra N, Beidas RS. Systematic review of clinician-directed nudges in healthcare contexts. *BMJ Open*. 2021;11(7):e048801.
52. Wallace DJ, Coleman Drake DM. Nudges in the Care of the Critically Ill. *Crit Care Med*. 2019;47(8):1150.
53. Thompson JD, Fish S, Ruiz E. Succinylcholine for endotracheal intubation. *Ann Emerg Med*. 1982;11(10):526–9.
54. April MD, Arana A, Pallin DJ, Schauer SG, Fantegrossi A, Fernandez J, et al. Emergency department intubation success with succinylcholine versus rocuronium: a National Emergency Airway Registry study. *Ann Emerg Med*. 2018;72(6):645–53.
55. Patanwala AE, Stahle SA, Sakles JC, Erstad BL. Comparison of succinylcholine and rocuronium for first-attempt intubation success in the emergency department. *Acad Emerg Med*. 2011;18(1):10–4.
56. Sagarin MJ, Barton ED, Chng Y-M, Walls RM, Investigators NEAR. Airway management by US and Canadian emergency medicine residents: a multicenter analysis of more than 6,000 endotracheal intubation attempts. *Ann Emerg Med*. 2005;46(4):328–36.
57. Avidan MS, Jacobsohn E, Glick D, Burnside BA, Zhang L, Villafranca A, et al. Prevention of intraoperative awareness in a high-risk surgical population. *N Engl J Med*. 2011;365(7):591–600.
58. Avidan MS, Zhang L, Burnside BA, Finkel KJ, Searleman AC, Selvidge JA, et al. Anesthesia awareness and the bispectral index. *N Engl J Med*. 2008;358(11):1097–108.
59. Brice D, Hetherington R, Utting J. A simple study of awareness and dreaming during anaesthesia. *BJA Br J Anaesth*. 1970;42(6):535–42.
60. Han JH, Vasilevskis EE, Schnelle JF, Shintani A, Dittus RS, Wilson A, et al. The diagnostic performance of the Richmond Agitation Sedation Scale for detecting delirium in older emergency department patients. *Acad Emerg Med*. 2015;22(7):878–82.
61. Diagnostic and Statistical Manual 5th Edition (DSM-5). Washington, DC: American Psychiatric Association. 2013;10:1176.
62. Jackson JC, Pandharipande PP, Girard TD, Brummel NE, Thompson JL, Hughes CG, et al. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. *Lancet Respir Med*. 2014;2(5):369–79.
63. Myles P, Williams D, Hendrata M, Anderson H, Weeks A. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10,811 patients. *Br J Anaesth*. 2000;84(1):6–10.
64. Dinglas VD, Faraone LN, Needham DM. Understanding patient-important outcomes after critical illness: a synthesis of recent qualitative, empirical, and consensus-related studies. *Curr Opin Crit Care*. 2018;24(5):401–9.
65. Needham DM, Sepulveda KA, Dinglas VD, Chessare CM, Friedman LA, Bingham CO III, et al. Core outcome measures for clinical research in acute respiratory failure survivors: An international modified delphi consensus study. *Am J Respir Crit Care Med*. 2017;196(9):1122–30.
66. American College of Emergency Physicians. Policy Statement. Mechanical Ventilation. 2017(October).
67. Cornelius T, Agarwal S, Garcia O, Chaplin W, Edmondson D, Chang BP. Development and validation of a measure to assess patients' threat perceptions in the emergency department. *Acad Emerg Med*. 2018;25(10):1098–106.
68. Sabapathi P, Roberts MB, Fuller BM, Puskarich MA, Jones CW, Kilgannon JH, et al. Validation of a 5-item tool to measure patient assessment of clinician compassion in the emergency department. *BMC Emerg Med*. 2019;19(1):1–7.
69. Homma K, Chang B, Shaffer J, Toledo B, Hefe B, Dalrymple N, et al. Association of social support during emergency department evaluation for acute coronary syndrome with subsequent posttraumatic stress symptoms. *J Behav Med*. 2016;39(5):823–31.
70. Reade MC, Finfer S. Sedation and delirium in the intensive care unit. *N Engl J Med*. 2014;370(5):444–54.
71. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208.
72. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377–81.
73. Larach MG, Klumpner TT, Brandom BW, Vaughn MT, Belani KG, Herlich A, et al. Succinylcholine use and dantrolene availability for malignant hyperthermia treatment: database analyses and systematic review. *Anesthesiology*. 2019;130(1):41–54.
74. Harper N, Cook T, Garcez T, Farmer L, Floss K, Marinho S, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and

- clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth.* 2018;121(1):159–71.
75. Barker D, D'Este C, Campbell MJ, McElduff P. Minimum number of clusters and comparison of analysis methods for cross sectional stepped wedge cluster randomised trials with binary outcomes: A simulation study. *Trials.* 2017;18(1):1–11.
 76. Li P, Redden DT. Small sample performance of bias-corrected sandwich estimators for cluster-randomized trials with binary outcomes. *Stat Med.* 2015;34(2):281–96.
 77. Kelly PJ, Baker AL, Deane FP, Callister R, Collins CE, Oldmeadow C, et al. Study protocol: a stepped wedge cluster randomised controlled trial of a healthy lifestyle intervention for people attending residential substance abuse treatment. *BMC Public Health.* 2015;15(1):1–9.
 78. Mouchoux C, Rippert P, Duclos A, Fassier T, Bonnefoy M, Comte B, et al. Impact of a multifaceted program to prevent postoperative delirium in the elderly: the CONFUCIUS stepped wedge protocol. *BMC Geriatr.* 2011;11(1):1–7.
 79. Gruber JS, Arnold BF, Reygadas F, Hubbard AE, Colford JM Jr. Estimation of treatment efficacy with complier average causal effects (CACE) in a randomized stepped wedge trial. *Am J Epidemiol.* 2014;179(9):1134–42.
 80. Nagelkerke N, Fidler V, Bernsen R, Borgdorff M. Estimating treatment effects in randomized clinical trials in the presence of non-compliance. *Stat Med.* 2000;19(14):1849–64.
 81. Terza JV. Simpler standard errors for two-stage optimization estimators. *Stand Genomic Sci.* 2016;16(2):368–85.
 82. Terza JV, Basu A, Rathouz PJ. Two-stage residual inclusion estimation: addressing endogeneity in health econometric modeling. *J Health Econ.* 2008;27(3):531–43.
 83. Blevins CA, Weathers FW, Davis MT, Witte TK, Domino JL. The post-traumatic stress disorder checklist for DSM-5 (PCL-5): Development and initial psychometric evaluation. *J Trauma Stress.* 2015;28(6):489–98.
 84. Weathers FW, Litz BT, Keane TM, Palmieri PA, Marx BP, Schnurr PP. The PTSD Checklist for DSM-5 (PCL-5). Scale available from the National Center for PTSD at www.ptsd.va.gov. 2013;10.
 85. Maslove DM, Leisman DE. Causal inference from observational data: New guidance from pulmonary, critical care, and sleep journals. *Crit Care Med.* 2019;47(1):1–2.
 86. Meli L, Kautz M, Julian J, Edmondson D, Sumner JA. The role of perceived threat during emergency department cardiac evaluation and the age-posttraumatic stress disorder link. *J Behav Med.* 2018;41(3):357–63.
 87. Griffiths J, Fortune G, Barber V, Young JD. The prevalence of post traumatic stress disorder in survivors of ICU treatment: a systematic review. *Intensive Care Med.* 2007;33(9):1506–18.
 88. Moss J, Roberts MB, Shea L, Jones CW, Kilgannon H, Edmondson DE, et al. Healthcare provider compassion is associated with lower PTSD symptoms among patients with life-threatening medical emergencies: a prospective cohort study. *Intensive Care Med.* 2019;45:1–8.
 89. Roberts AL, Gilman SE, Breslau J, Breslau N, Koenen KC. Race/ethnic differences in exposure to traumatic events, development of post-traumatic stress disorder, and treatment-seeking for post-traumatic stress disorder in the United States. *Psychol Med.* 2011;41(1):71.
 90. Alim TN, Graves E, Mellman TA, Aigbogun N, Gray E, Lawson W, et al. Trauma exposure, posttraumatic stress disorder and depression in an African-American primary care population. *J Natl Med Assoc.* 2006;98(10):1630.
 91. Hatch SL, Dohrenwend BP. Distribution of traumatic and other stressful life events by race/ethnicity, gender, SES and age: A review of the research. *Am J Community Psychol.* 2007;40(3–4):313–32.
 92. Hayes AF, Scharkow M. The relative trustworthiness of inferential tests of the indirect effect in statistical mediation analysis: Does method really matter? *Psychol Sci.* 2013;24(10):1918–27.
 93. MacKinnon DP, Krull JL, Lockwood CM. Equivalence of the mediation, confounding and suppression effect. *Prev Sci.* 2000;1(4):173–81.
 94. Gulliford M, Adams G, Ukoumunne O, Latinovic R, Chinn S, Campbell M. Intraclass correlation coefficient and outcome prevalence are associated in clustered binary data. *J Clin Epidemiol.* 2005;58(3):246–51.
 95. Sandin RH, Enlund G, Samuelsson P, Lenmarken C. Awareness during anaesthesia: a prospective case study. *The Lancet.* 2000;355(9205):707–11.
 96. Zhang C, Liang X, Sun Y-X, Li Y-H, Zhang L, Feng C-S, et al. Bispectral index monitoring prevent awareness during total intravenous anesthesia: a prospective, randomized, double-blinded, multi-center controlled trial. *Chinese Med J.* 2011;124(22):3664–9.
 97. Vittinghoff E, Sen S, McCulloch C. Sample size calculations for evaluating mediation. *Stat Med.* 2009;28(4):541–57.
 98. Fritz MS, MacKinnon DP. Required sample size to detect the mediated effect. *Psychol Sci.* 2007;18(3):233–9.
 99. Driver BE, Prekker ME, Klein LR, Reardon RF, Miner JR, Fagerstrom ET, et al. Effect of use of a bougie vs endotracheal tube and stylet on first-attempt intubation success among patients with difficult airways undergoing emergency intubation: a randomized clinical trial. *JAMA.* 2018;319(21):2179–89.
 100. Fuller BM, Ferguson IT, Mohr NM, Drewry AM, Palmer C, Wessman BT, et al. Lung-protective ventilation initiated in the emergency department (LOV-ED): a quasi-experimental, before-after trial. *Ann Emerg Med.* 2017;70(3):406–18 (PMCID: PMC5573637).
 101. Prekker ME, Donelan C, Ambur S, Driver BE, O'Brien-Lambert A, Hottinger DG, et al. Adoption of low tidal volume ventilation in the emergency department: A quality improvement intervention. *Amer J Emerg Med.* 2020;38(4):763–7.
 102. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. *Bmj.* 2015;350:h2147.
 103. Hemming K, Taljaard M, McKenzie JE, Hooper R, Copas A, Thompson JA, et al. Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration. *Bmj.* 2018;363:k1614.
 104. Jackson JC, Hart RP, Gordon SM, Hopkins RO, Girard TD, Ely E. Post-traumatic stress disorder and post-traumatic stress symptoms following critical illness in medical intensive care unit patients: assessing the magnitude of the problem. *Crit Care.* 2007;11(1):1–11.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

