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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)

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ABSTRACT

Introduction Sedation is a cornerstone therapy in the management of patients receiving mechanical ventilation and is highly influential on outcome. Early sedation depth appears especially influential, as early deep sedation is associated with worse outcome when compared with light sedation. Our research group has shown that patients receiving mechanical ventilation in the emergency department (ED) are exposed to deep sedation commonly, and ED sedation depth is impactful on intensive care unit (ICU) care and clinical outcomes. While extensive investigation has occurred for patients in the ICU, comparatively little data exist from the ED. Given the influence that ED sedation seems to carry, as well as a lack of ED-based sedation trials, there is significant rationale to investigate ED-based sedation as a means to improve outcome.

Methods and analysis This is a multicentre (n=3) prospective, before-and-after pilot trial examining the feasibility of implementing targeted sedation in the immediate postintubation period in the ED. A cohort of 344 patients receiving mechanical ventilation in ED will be included. Feasibility outcomes include: (1) participant recruitment; (2) proportion of Richmond Agitation-Sedation Scale (RASS) scores in the deep sedation range; (3) reliability (agreement) of RASS measurements performed by bedside ED nurses; and (4) adverse events. The proportion of deep sedation measurements before and after the intervention will be compared using the χ^2 test. Logistic regression will be used to compare before-and-after differences, adjusting for potential confounders. The inter-rater correlation coefficient will be used to assess paired observations between a study team member and bedside ED nurses, and to describe reliability of RASS measurements.

Ethics and dissemination The Human Research Protection Office at Washington University in St. Louis School of Medicine has approved the study. The

Strengths and limitations of this study

► This study will generate new knowledge about an influential component of supportive care (sedation in the emergency department (ED)) that may be contributing to poor outcomes.
► The study challenges the historical paradigm of deep sedation in the ED by targeting light sedation in the immediate postintubation phase of care.
► The pragmatic design will assure all consecutive patients meeting eligibility criteria will be enrolled, enhancing external validity.
► Uptake of the protocol may prove more difficult than anticipated, hindering the ability to target sedation in the ED.

publication of peer-reviewed manuscripts and the presentation of abstracts at scientific meetings will be used to disseminate the work.
Registration ClinicalTrials.gov identifier NCT04410783; Pre-results.

INTRODUCTION
Background and rationale

Acute respiratory failure requiring mechanical ventilation in the emergency department (ED) is required for more than 250 000 patients annually in the USA; over 30% of these patients will die.[1–6] This rate can exceed 50% if acute respiratory distress syndrome develops after admission.[3] Even if patients survive, they experience staggering morbidity in terms of hospitalisation days, high readmission rates, cognitive decline, psychological dysfunction and lengthy rehabilitation.[7–12]

Despite these facts, outcomes for critically ill patients have improved over the past three decades, largely from improving the delivery of critical care and optimising supportive therapies (eg, lung-protective ventilation, fluid management, awakening and breathing trials, early mobility, etc).[13–16]

Sedation management is a cornerstone therapy for patients receiving mechanical ventilation, and is highly influential on outcome. Current sedation guidelines suggest targeting light levels of sedation depth, unless clinically indicated otherwise.[16] However, the incidence of deep sedation in the intensive care unit (ICU) is high (up to 70%), and clinicians frequently extend periods of deep sedation for days.[17] The deep sedation provided to patients receiving mechanical ventilation is troubling when considering consequences of deep sedation. Deep sedation has been associated with an increased incidence of: (1) ventilator-associated pneumonia[18 19]; (2) aspiration[20]; (3) gastrointestinal dysfunction[21 22]; and (4) deep venous thrombosis.[23] Most relevant to the current work, these clinical sequela occur early, within 1–2 days, and provide strong clinical rationale for the avoidance of deep sedation during the early period of critical illness when possible.[19 23 24] With respect to patient-oriented outcomes, deep sedation has a negative impact as shown by greater: (1) mortality; (2) mechanical ventilation, ICU and hospital duration; and (3) incidence of post-traumatic stress disorder, delirium and coma.[15 25–31] Early sedation depth may be especially consequential. Three cohort studies from the ICU found deep sedation during the initial 48 hours of mechanical ventilation to be common and associated with increased mechanical ventilation duration, mortality, incidence of delirium and longer lengths of stay.[32–34] Two pilot trials, not powered for clinical endpoints, showed a trend of more delirium, ventilation time and lengths of stay associated with early deep sedation.[35 36] To collate the literature regarding early sedation and its potential impact on outcome, our research group conducted a comprehensive systematic review and meta-analysis, which demonstrated that early light sedation, compared with deep sedation, was associated with: (1) lower mortality; (2) less delirium; and (3) fewer ventilator days.[37]

The ED could be a high-yield clinical arena in which to target sedation depth to improve outcome. In a single-centre study, our group demonstrated an incidence of deep sedation of 64%, and an association between deep sedation and: (1) increased mortality; (2) fewer ventilator-free days; and (3) longer lengths of stay.[38] There was a depth-dependent relationship between ED sedation and outcome such that there were improved outcomes associated with incrementally lighter ED sedation depth. To build on this single-centre experience, the multicentre (n=15) ED-SED Study was a prospective cohort study conducted to examine practice patterns and clinical outcomes associated with ED sedation across a diverse sample of medical centres in the USA.[39] The incidence of deep sedation (Richmond Agitation-Sedation

Scale (RASS) of −3 to −5) in the ED was 53%, and deep sedation in the ED predicted the receipt of deep sedation during the first 48 hours in the ICU. ED deep sedation was also associated with 1.9 fewer ventilator-free days (−0.40 to 4.13), 2.3 fewer hospital-free days (0.26–4.32) and a 13.1% higher incidence of acute brain dysfunction (delirium+coma, odds ratio (95% CI) 1.73 (1.10–2.73)). Despite this, no ED-based sedation trial has been conducted, and emergency medicine-based policy statements mention nothing regarding light sedation as a potential therapeutic target.[40] These facts suggest that sedation has historically been viewed as an 'ICU issue' and given low priority in the setting of early critical illness. However, inadequate sedation is not without consequence, as it may increase physiologic stress, catecholamine release, oxygen consumption and recall of stressful memories.[41–44] Therefore, whether deep sedation in the immediate postintubation period in the ED is associated with worse outcome remains unclear.

Given the abundance of data showing a strong association between early deep sedation and clinical outcomes, the lack of clinical trials targeting sedation in the ED, and the increase use of the ED (in terms of patient visits and boarding hours) for critically ill patients, there is significant rationale to conduct an ED-based sedation trial in order to improve outcome.[45] Furthermore, given the influence of ED sedation depth on early ICU sedation, targeted sedation in the ED could carry benefit, even for healthcare systems with relatively short ED lengths of stay. Prior to proceeding with a large-scale clinical trial, our research team designed the ED-SED Pilot Trial to fill critical information gaps. The objective of the ED-SED Pilot Trial is to examine the feasibility of implementing ED-based goal-oriented sedation, which targets light sedation as the default approach, in patients receiving mechanical ventilation. We hypothesise that ED-based goal-oriented sedation will be feasible in terms of: (1) trial recruitment; (2) efficacy in achieving target sedation; (3) reliability of RASS measurements during routine care in the ED; (4) adverse events; and (5) barriers to implementation.

METHODS AND ANALYSIS
Study design
This is a multicentre (n=3), prospective before-and-after trial, and is reported in compliance with the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) statement (see online supplemental file 1). A schematic of the before-and-after trial design appears in figure 1. Data collection in the before phase is planned to begin in August of 2020; data collection in the after phase is anticipated to be completed in September of 2021.

Study population
This trial will target adult patients receiving mechanical ventilation in the ED. Inclusion criteria are: (1) mechanical ventilation via an endotracheal tube, including patients intubated in the ED and prior to arrival (ie,
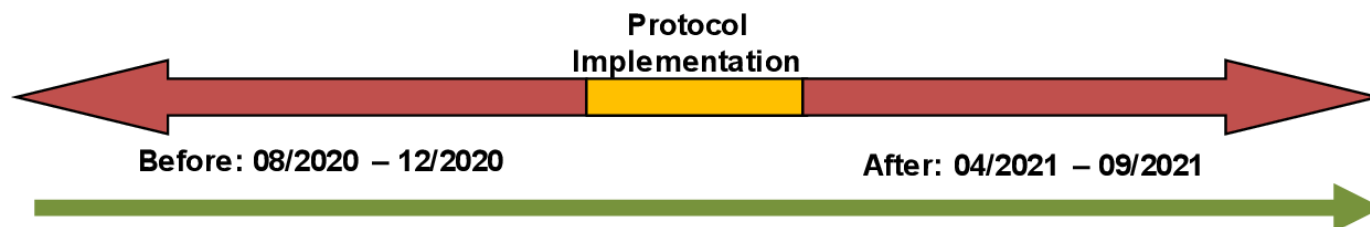
Figure 1 Schematic of the prospective, before-and-after trial design.

prehospital); and (2) age ≥18 years. Exclusion criteria are: (1) acute neurologic injury (stroke, intracranial haemorrhage, traumatic brain injury, cardiac arrest, status epilepticus, fulminant hepatic failure); (2) ongoing neuromuscular blockade; (3) transfer directly from the ED to the operating room, or other procedural areas; (4) death or transition to comfort measures within 24 hours; (5) transfer to another hospital from the ED; and (6) chronic/home mechanical ventilation.

Patients will be recruited from the ED at three academic medical centres in the USA: (1) Barnes-Jewish Hospital/Washington University School of Medicine, St. Louis, Missouri; (2) University of Iowa, Iowa City, Iowa; and (3) Cooper Medical School of Rowan University, Camden, New Jersey. Patients receiving mechanical ventilation 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 enrolment of women will be approximately 45% and the enrolment of minorities will be approximately 35% African-American 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 patients presenting to the ED requiring mechanical ventilation in three academic centres. Each site has a system in place for real-time alerts (24 hours/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 patients receiving mechanical ventilation presenting to the ED.[39] All patients who satisfy inclusion and exclusion criteria will be enroled.

Patient and public involvement
The patients in this study were not involved in the development of the research question or study design, and will not be involved in recruitment or conduct of the study.

Interventions
Patients in the before phase of the trial will receive usual care, which is clinician-directed sedation after the initiation of mechanical ventilation. A pragmatic approach will be used, and other cointerventions will be at the discretion of the treating clinician and will not be standardised.

After half of the patients have been enroled, the before phase will end and enrolment will be suspended for a 3-month execution of the protocol implementation phase. This is an educational initiative aimed at improving how existing sedation protocols are delivered to patients receiving mechanical ventilation in the ED. During this implementation phase, the study team will engage key stakeholders (ie, nursing leadership, nurses, attending and resident physicians) regarding our clinical outcome data on the importance of an ED-based sedation protocol, and the objectives of the research. We will educate with in-person training (ie, in-services and lectures) and computer-based educational strategies (eg, www.icudelirium.org) focused on the importance of sedation protocols and sedation depth on patient outcome, aspects of the protocol related to medication titration, and sedation assessment with RASS. We will also strategically place marketing tools, such as graphics and pocket cards, throughout the ED. We will evaluate the use of sedation throughout the study in order to better understand providers' perception of and experience with ED-based sedation protocols. This will include informal interactions regarding the progress of adhering to sedation recommendations and ongoing support throughout the study. We will also conduct a qualitative sedation knowledge and impediment survey in order to interpret study results through the lens of qualitative findings, and to better understand facilitators and barriers to sedation protocol implementation. These surveys will assess providers' perception of sedation, and other aspects of daily practice, which are vital in protocol implementation (ie, support, teamwork, resource availability).[46] The survey will be administered prior to the after phase of the trial, and following completion of patient enrolment (see online supplemental file 2).

The implementation phase is needed for two primary reasons. First, while sedation is standard care for patients receiving mechanical ventilation, the overwhelming majority of data comes from the ICU.[16] The lack of emphasis on ED-based sedation is likely driven by: (1) comparatively sparse data from the ED domain; and (2) clinical differences, at times vast, between the two locations (ie, nurse-to-patient ratios, acuity, physician staffing). Therefore, implementation must proceed in a way that is feasible and balances clinical realities in a way that is both provider and patient oriented. Implementation will proceed such that provider feedback is solicited so that targeted sedation is effectively used in the ED, allowing us to test the intervention under real-world conditions. Second, during implementation, sites will not be considered as exposed or not exposed, allowing mitigation of

contamination risk. To maintain a pragmatic approach to the study, and because the sedation recommendations are quite similar across sites, this study will not alter anything about the post-intubation care at a site (ie, medications delivered). It will only educate providers on the importance of using a sedation protocol effectively, including: (1) addressing pain first; (2) setting a target sedation depth; (3) targeting a light sedation depth (RASS −2 to 0) as the default approach; and (4) appropriately titrated sedation.

After the 3-month implementation phase, we will resume enrolment, and these subjects will comprise the after phase of the study. Participants in the after phase will also receive standard postintubation care at the discretion of the treating team, though it will be after the education initiative aimed at improving sedation practices in the ED. While light sedation (RASS 0 to −2) will be emphasised during the education initiative as the most appropriate approach for the majority of patients, patients will be treated and sedated at the discretion of the clinical team. During the after phase, routine monitoring of sedation practices will occur.

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. The location of intubation will be collected (ie, ED, prehospital, outside hospital/other facility), as will drugs used to facilitate intubation, and ventilator settings. After the initiation of mechanical ventilation in the ED, all medications related to analgesia and sedation in the ED will be collected, and will include opiates, benzodiazepines, propofol, ketamine, dexmedetomidine, etomidate, haloperidol, quetiapine and neuromuscular blockers. Sedation depth in the ED will be recorded by bedside nurses, using RASS.[47]

The following in-hospital data will be collected: duration of ventilation, agents used for analgesia and sedation during the first 48 hours of ICU admission, depth of sedation during the first 7 days of ICU admission, incidence of acute brain dysfunction, lengths of stay in the ICU and hospital, discharge location and mortality status. Table 1 shows a description of events for this study.

A data and safety monitoring board (DSMB), independent of the research team and funder, will be used to monitor the data. The DSMB will assess safety and efficacy of study procedures, and monitoring the overall conduct of the study. The DSMB also will review adverse event data, other safety data, quality and completeness of study data, protocol adherence data and enrolment data at each meeting to ensure proper trial conduct and

Table 1 Schedule of events for this prospective, before-and-after trial

Measurement/event	0*	1	2	3	4	5	6	7	Hosp D/C
Inclusion/exclusion criteria	X								
Demographics	X								
Comorbid conditions	X								
Height, weight, PBW, BMI	X								
Vital signs and pertinent labs	X								
Illness severity—SOFA	X								
Intubation details	X								
Ventilator settings and data	X								
ED process of care variables	X								
Adverse events†	X								
Medications for sedation	X	X	X						
RASS measurements	X	X	X	X	X	X	X	X	
Incidence of deep sedation	X	X	X	X	X	X	X	X	
Blood gas assessment	X	X	X						
Delirium assessment, CAM-ICU	X	X	X	X	X	X	X	X	
Ventilator status									X
Length of stay (hospital and healthcare facility)									X
Discharge location									X
Mortality status									X

*Day 0 refers to the ED.
†Inadvertent extubation, device removal, awareness with paralysis.
BMI, body mass index; CAM, confusion assessment method; ED, emergency department; ICU, intensive care unit; PBW, predicted body weight; RASS, richmond agitation-sedation scale; SOFA, sequential organ failure assessment.

continued feasibility of answering the research questions. Meetings between the research team and the DSMB will occur before the study begins, on completion of the before phase of enrolment, after half of the patients in the after phase have been enroled, and on study completion. As this is a pilot trial primarily aimed at assessing feasibility, there will be no stopping guidelines for the study.

Outcomes

Several overarching themes exist as reasons to conduct pilot studies, including those related to process, resources, management and intervention effects.[48] The main purpose of this pilot study relates to process. Therefore, the outcome measures revolve around feasibility, not clinical outcomes, and this pilot and its outcome measures have been designed to specifically address the unanswered questions that remain despite our preliminary data. Quantitative feasibility outcomes include: (1) participant recruitment; (2) proportion of RASS scores in the deep sedation range; (3) reliability (agreement) of RASS measurements performed by bedside ED nurses and study team members; and (4) adverse events. These data will be supplemented with a qualitative assessment of barriers to implementation (survey of nurses and physicians). While the main purpose of the study is to test feasibility, we will also collect clinical outcome data and adverse events potentially related to ED-based sedation (inadvertent extubation, device removal and awareness with paralysis).

Proposed statistical methods

This pilot study was designed to test our procedures and estimate the proportions of our participants who would meet our feasibility objectives in a powered clinical trial. Therefore, the data analyses are mostly descriptive. Demographic and treatment variables, as well as participant characteristics, will be summarised by using descriptive statistics such as mean (SD) and median (IQR) for continuous variables, and frequency distributions for categorical variables.

For recruitment rate and adverse events, the type of data will include Poisson count and binary. Point estimates and confidence intervals will be presented for data analyses. Based on empirical data, the methods for confidence intervals may be based on the normal distribution approximation to Poisson/binomial distribution (when Poisson mean >10 or the number of binomial events >10), or the exact method (when Poisson mean or number of binomial events is small). The proportion of deep sedation measurements before and after the intervention will be compared using the χ^2 test to compare two independent proportions. Logistic regression will be used to compare before-and-after differences, adjusting for potential confounders. The inter-rater correlation coefficient will be used to assess paired observations between a study team member and bedside ED nurses, and to describe reliability of RASS measurements (continuous

scale). Two-way random effects, in which two raters in each site (ie, study team member and bedside ED nurse) are considered as a random sample from a larger population, will be used.[49] Point estimates of inter-rater correlation coefficient and 95% CIs will be presented. Regarding the survey results describing potential barriers to the implementation, these data will be summarised and reported as frequencies and proportions, and responses from time 1 (before protocol) will be compared with time 2 (after completion of the pilot study). Using inductive content analysis, free text from open-ended questions will be systematically reviewed line by line to identify themes around sedation protocol use.[50] All tests will be two-tailed, and a p value <0.05 will be considered statistically significant.

Sample size

The sample size is based on the proportion of RASS scores in the deep sedation range, as that is most applicable in assessing protocol success. Our preliminary data from the three sites in the ED-SED Pilot Trial demonstrate that 63% of RASS assessments are expected to be in the deep sedation range. We assume an effect size (absolute proportion difference) of 15% (ie, deep sedation 63% in the before phase and 48% in the after phase), which is: (1) within the expected range based on an ICU sedation trial which targeted light sedation[35]; (2) feasible to attain; and (3) a clinically meaningful demonstration of adherence to light sedation per the protocol. Assuming α=0.05 and power=0.80 (two-tailed), 172 patients will be needed in each phase, that is, a total of 344 patients.

For the reliability aim of the study, a convenience sample of 25 patients at each site will be used. The RASS takes less than 20 s to perform, requires minimal training and has been shown to be highly reliable among multiple types of healthcare professionals.[51 52] Paired observations of two raters will be conducted on each patient: a study team member and the bedside ED nurse. The sample size determination is based on the precision of inter-rater correlation coefficient estimates. With a desired sample inter-rater correlation coefficient of 0.95, 23 patients in each site are needed to produce a one-sided 95% CI with a lower bound of 0.90, which indicates 'excellent' reliability. With a sample of 25 patients at each site, there will be high precision in the estimation of agreement in RASS measurements between study team members and bedside ED nurses in the after phase of the trial.

Anticipated results

The goal enrolment is 0.3 patients per day at each site. This is realistic given the nature of the trial design for this pilot and the future trial, and based on the previous experience of members of the research team in studying patients receiving mechanical ventilation in ED.[2–5 39 53] With successful implementation of targeted sedation in the ED, we expect to: (1) achieve a 15% reduction in the proportion of RASS scores in the deep sedation range; and (2) demonstrate high agreement among RASS

assessments between trained study team members and bedside ED nurses. Guidelines recommend sedation protocols and light sedation in patients receiving mechanical ventilation because of a favourable risk-to-benefit ratio, with consistent data showing improved outcomes.[16] However, as a trial such as this has not previously been conducted in the ED, tracking adverse events will be vital for patient safety and clinical trial planning. We expect the incidence of adverse events to be similar between the before and after groups, with the following baseline expected event rates: self-extubation (<1%),[54 55] device removal (eg, urinary catheter, venous or arterial access, enteric tubes (1%–2%))[56] and awareness with paralysis (~1%).[57 58]

Data storage and management

All data will be entered by the study team and data accuracy will be verified by the study principal investigator (PI). Data quality control measures will include queries to identify missing data, outliers and discrepancies. Only study team members will have access to protected health information. After enrolment, a unique identifier will be assigned to each study subject. The data will be uploaded and stored using Research Electronic Data Capture (REDCap), a web-based data management application. All computers will be password-protected and encrypted per university policy. We will ensure that the anonymity is maintained. Patients will not be identified by name in any reports on this study. The study PI will have access to the final study dataset.

Ethics and dissemination
Ethics approval

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, and will be conducted with waiver of informed consent.

Dissemination and data sharing

Sharing of data generated by this trial is an important part of the proposed activities. Data will be shared with other investigators through academically established means, as necessary and appropriate. Datasets generated from the trial will be available from the overall study PI on reasonable request. Collaboration with others investigators is encouraged. The results will be disseminated via publication in a peer-reviewed journal and presentation at national meetings.

Strengths and limitations
Strengths

The genesis of early sedation is in the ED, and our preliminary data suggest that optimisation of ED-based sedation could improve both early ICU sedation and patient-oriented clinical outcomes. Therefore, we believe the most high impact approach is to focus and initiate future investigations in the ED domain. Given the

lack of ED-based clinical sedation trials that have been conducted, the ED-SED Pilot Trial was designed to assess feasibility of implementing targeted sedation in the ED in preparation for a large-scale clinical trial.

The study has several strengths. It aims to identify a new potential therapeutic target (ie, targeted sedation) in immediate postintubation care. Deep sedation has been the default, especially during the early period of mechanical ventilation, as shown by a number of studies.[32 33 59] Rather than studying a completely new therapy, the proposed study will generate new knowledge about a standard component of supportive care that may already be contributing to poor outcomes. Furthermore, we propose a proactive approach to targeted sedation during the most acute phase of respiratory failure. The historical paradigm has focused on reactive interventions to reverse unresponsiveness, as most sedation trials have waited 48–96 hours before randomisation and study initiation.[15 25 30 60–62]

Our study also differs from a recent early ICU sedation trial in several ways.[63] First, the ED-SED Pilot will account for both ED and ICU sedation, as opposed to ICU sedation only. Second, sedation depth will be the target, as opposed to a particular drug (eg, dexmedetomidine), as it is possible that targeting light sedation in the ED, where it has not been the norm, will be more impactful and achieve greater separation in the first days of ICU care. Third, the pragmatic design will assure that all consecutive patients meeting eligibility criteria will be enroled, which will generate data that are more externally valid.

Limitations

This study also has several limitations. Protocol uptake may be suboptimal and implementation may be more difficult than anticipated. A documented decrease in the proportion of RASS measurements in the deep sedation range will be vital to demonstrate feasibility. We believe this is possible for several reasons. We will assess provider perceptions regarding the protocol with a qualitative survey that is administered before and after enrolment. This will allow modifications of the ED-SED Protocol if themes regarding non-adherence to the protocol are identified. Targeted sedation protocols have been successfully implemented in the ICU setting for years. While the ED environment is unique, there is no empiric reason to believe that sedation protocols would be inherently difficult to implement in the ED. The agreement in RASS assessments between trained study team members and bedside ED nurses may be low. This lack of fidelity would hinder our ability to conduct a large-scale clinical trial across multiple sites. While RASS has not been examined in the ED in a similar context as this pilot, there is extensive ICU data demonstrating excellent inter-rater reliability among multiple types of healthcare providers. Given the fact that this aspect of the ED-SED Pilot is also quite simple (RASS takes <20s to perform) and reliable, we anticipate similar success. From a methodology standpoint, before-and-after studies are prone to temporal

changes and imbalance between study groups. The relatively short duration of enrolment and pre-existing standardisation of cointerventions suggests this will not occur, but any imbalances will be reported. The enrolment window for the before and after periods may lead to seasonal imbalances regarding indications leading to respiratory failure in the ED. However, our prior work has not revealed this to be very significant.[2] The study design limits any associations between any interventions and outcomes, and will also not be powered for clinical outcomes. This is not the primary intent of this investigation, but rather to assess feasibility in order to better plan for a larger trial. In that regard, the ED-SED Pilot could be a pivotal trial in the process of optimising ED-based postintubation care in order to reduce adverse events and improve clinical outcome.

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