The Emergency Department Sedation Pilot Trial

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The ED-SED Pilot: a Multicenter, Before-After Study to Improve Sedation in the Emergency Department

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1 ABBREVIATIONS AND DEFINITIONS

ACCM = American College of Critical Care Medicine
AE = Adverse Event
AIDS = Acquired Immune Deficiency Syndrome
BMI = Body Mass Index
CAM = Confusion Assessment Method
COPD = Chronic Obstructive Pulmonary Disease
CI = Confidence Interval
DSMB = Data Safety Monitoring Board
ED = Emergency Department
ED-SED = Emergency Department Sedation
GCS = Glasgow Coma Scale
HIPAA = Health Insurance Portability and Accountability Act
ICC = Interrater Correlation Coefficient
IRB = Institutional Review Board
ICU = Intensive Care Unit
IRB = Institutional Review Board
NIH = National Institutes of Health
OR = Odds Ratio
PBW = Predicted Body Weight
PHI = Protected Health Information
PI = Principal Investigator
RASS = Richmond Agitation Sedation Scale
RCT = Randomized Controlled Trial
REDCap = Research Electronic Data Capture
SAE = Serious Adverse Event
SAS = Statistical Analysis Software
SOFA = Sequential Organ Failure Assessment
US = United States
VFD = Ventilator-free days

2 STUDY SUMMARY

2.1 Title

The ED-SED Pilot: a Multicenter, Before-After Study to Improve Sedation in the Emergency Department

2.2 Objective

To assess the impact of an educational intervention on the delivery of post-intubation sedation in the ED.

2.3 Hypothesis

Feasibility of adhering to goal-oriented sedation in the ED will be demonstrated by: 1) effective trial recruitment; 2) efficacy in achieving target sedation; 3) reliability of RASS measurements during routine care in the ED; and 4) a low and similar incidence of adverse events.

2.4 Study Design and Synopsis

The ED-SED Pilot is a multicenter, prospective, observational before-and-after study conducted on 400 mechanically ventilated ED patients at three academic medical centers: Washington University in St. Louis School of Medicine (St. Louis, MO), Cooper Hospital of Rowan University (Camden, NJ), and University of Iowa Carver College of Medicine (Iowa City, IA). In addition, we will conduct a survey on an estimated 300 nurses and physicians.

We will screen all mechanically ventilated ED patients for study eligibility and will enroll all consecutive patients satisfying inclusion and exclusion criteria. The study will be conducted with waiver of informed consent.
In the before phase of the study, patients will receive usual care, which is clinician-directed sedation after the initiation of mechanical ventilation. After 200 patients have been enrolled in the before phase, we will begin an education implementation initiative for three months. Sedation protocols are already part of routine post-intubation care for mechanically ventilated patients, yet our data demonstrate that sedation protocols are not being effectively used. This study aims to improve the quality of post-intubation sedation by educating caregivers on the post-intubation sedation protocols which are already in place for mechanically ventilated patients, and studying that process in a rigorous fashion. After the education initiative, we will resume enrollment, and these patients will comprise the after phase of the study. The over-arching purpose of this study is to assess the impact that our educational initiative has on post-intubation sedation practices in the ED

The primary outcome measures are related to feasibility and include: 1) participant recruitment; 2) proportion of RASS scores in the deep sedation range; 3) reliability of RASS measurements during routine care in the ED; and 4) adverse events. To better assess potential facilitators and barriers to adherence to guideline-supported sedation recommendations, we will also conduct a qualitative assessment (i.e. survey) of nurses and physicians. The study is intended to be pragmatic, so patient-level data will be easily accessible from the electronic medical record.

2.5 Inclusion Criteria

1. Mechanical ventilation via an endotracheal tube.
2. Age ≥ 18 years.

2.6 Exclusion Criteria

1. Acute neurologic injury (stroke, intracranial hemorrhage, traumatic brain injury, cardiac arrest, status epilepticus, fulminant hepatic failure).
2. Ongoing neuromuscular blockade.
3. Death or transition to comfort measures within 24 hours.
4. Transfer to another hospital from the ED.
5. Chronic/home mechanical ventilation.
6. Transfer directly from the ED to the operating room.

2.7 Randomization and Study Initiation Time Window

This is a prospective, observational, before-and-after study with no randomization. Consecutive mechanically ventilated patients, satisfying inclusion and exclusion criteria, will be studied. Enrollment and pertinent data (see below) collection will be initiated and obtained from the patient's ED stay.

2.8 Primary Outcomes

This study aims to improve the quality of post-intubation sedation by educating caregivers on the post-intubation sedation protocols which are already in place for mechanically ventilated patients. The outcome measures revolve around feasibility, and not clinical outcomes. Quantitative outcomes include: 1) participant recruitment; 2) proportion of RASS scores in the deep sedation range; 3) reliability of RASS measurements during routine care in the ED; and 4) adverse events. These data will be supplemented with a qualitative survey of nurses and physicians to assess facilitators and barriers to adherence to guideline-supported sedation recommendations. The primary analysis and sample size calculation will be based on the proportion of RASS scores in the deep sedation range, as a reflection of success of our sedation education initiative.

2.9 Secondary Outcomes

We will also collect clinical outcome data, including: 1) duration of mechanical ventilation; 2) duration of stay in the ICU and hospital; 3) incidence of acute brain dysfunction (i.e. delirium and coma); and 4) mortality.

2.10 Sample Size and Interim Monitoring

We base our sample size calculation on the proportion of RASS scores in the deep sedation range as that is most applicable in assessing success of our education initiative. Our preliminary data from the three sites in this pilot proposal demonstrate that 63% of RASS assessments will be in the deep sedation range. We assume an effect size (proportion difference) of 15% (i.e. deep sedation in 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 [1]; 2) feasible to attain; and 3) a clinically meaningful demonstration of adherence to goal-directed sedation. Assuming $\alpha=0.05$ and power=0.80 (two-tailed), we calculate that 200 patients will be needed in each phase, i.e. a total of 400 patients.

An institutional DSMB at Washington University in St. Louis will be used for this study. It will consist of a small group of experts independent of the study, including a biostatistician, emergency physician, and pulmonary-critical care physician. The PI and the study team will prepare summary reports for the DSMB at the end of the before phase. During the after phase, the DSMB will review the prepared study data for safety every month to make sure there is not a spike in any adverse events. As this is a pilot trial, there will be no formal statistical tests for stopping rules, so recommendations by the DSMB will be made based on the assessment of clinical outcomes and human subject risk. Given the risk of deep sedation as documented in the medical literature, our own preliminary data, and the very low event rates for adverse events described in this population, we believe the risk: benefit ratio of this proposal is favorable. In addition, we estimate that approximately 300 nurses and physicians will respond to the survey (total number in the study= 700).

3 TRIAL DESCRIPTION

3.1 Background

Annually, approximately 300,000 patients receive mechanical ventilation in U.S. emergency departments (ED), many of whom have protracted lengths of stay while awaiting ICU admission[2]. Up to 30% of these patients will die and 25% of survivors are readmitted to the hospital within 30 days [2-6]. Effective therapies to reduce morbidity and mortality in this cohort have been limited. However, the ED now appears to be an effective arena to optimize outcomes for mechanically ventilated patients. As an example, our group has shown that lung-protective ventilation initiated in the ED can reduce pulmonary complications, mortality, and lengths of stay [3].

Optimized sedation, with the use of sedation protocols, is highly recommended to reduce complications and improve outcome in critically ill mechanically ventilated patients. As an example, improved sedation practice with the use of protocols has been shown to reduce the duration of mechanical ventilation, lengths of stay in the ICU and hospital, sedative dose, pneumonia, and mortality, with no impact on adverse events, such as inadvertent extubation [7-22]. As a result, the American College of Critical Care Medicine Practice Guidelines for the Management of Pain, Agitation, and Delirium recommend: 1) “an assessment-driven, protocol-based, stepwise approach for pain and sedation management in critically ill adults”; and 2) “clinicians should target a light rather than deep level of sedation in their intubated, critically ill adult patients, unless deeper sedation is clinically indicated”.

As a summary, based on over 20 years of research in this field, extensive evidence supports the fact that the best practice for mechanically ventilated patients is the use of goal-oriented sedation protocols which favor light (versus deep) sedation targets when possible.

Despite the existing data and guideline recommendations, there has been an overall lack of data regarding the early period of mechanical ventilation in the ED, yet this time frame may be particularly influential on outcome [23]. Retrospective, observational data from our center indicate that deep sedation in the ED is common in mechanically ventilated patients and a key risk factor for mortality and longer lengths of stay [24]. In a comprehensive systematic review and meta-analysis, we showed a strong association between early (i.e. within 48 hours of instituting mechanical ventilation) sedation depth and outcome [23]. Finally, in a prospective, multi-center cohort study (The ED-SED Study), we demonstrated again that deep sedation in the ED was common and negatively associated with patient-oriented clinical outcomes [25]. This suggests that, despite the existence of ED-based sedation protocols for mechanically ventilated patients, these sedation protocols are not being followed in the ED setting. Therefore, the ED-SED Pilot is needed to assess the impact of an educational initiative aimed at improving sedation practices by improving adherence to guideline-recommended sedation care in the post-intubation period.

3.1.1 Background on the three ED-SED Pilot Sites

Similar to other EDs from the multicenter ED-SED Study, and published data from the ICU domain, the three sites in the ED-SED Pilot primarily sedate mechanically ventilated patients with some combination of fentanyl, propofol, and midazolam, via the use of existing sedation protocols and/or order sets in the electronic medical record [25-28] (See Table). An example of the sedation protocols from each site is included in the Appendix, and this demonstrates similarities among each site, including medications used, addressing pain first, and targeted sedation based on a goal sedation depth. This background information also demonstrates that post-intubation sedation at each site is standard, and that the current study will not be introducing any new therapy into the routine care of the patients, yet attempting to optimize (via education) the care that is already in place.

Table 1. Sedation practices at the three ED-SED Pilot sites

Site	Description	Sedation protocol /order set in place?	Deep sedation incidence %*	Drug n (%) Cumulative dose Weight-based dose				
				Fentanyl	Propofol	Midazolam	No analgesia	No sedation
Cooper University Hospital	Academic, urban, level 1 trauma	Yes	51.7	21 (35.0) 200 (96 - 525) 2.4 (1.1 - 7.6)	50 (83.3) 386 (168 - 1061) 5.4 (2.4 - 13.4)	12 (20.0) 4.0 (4.0 - 5.8) 0.05 (0.04 - 0.08)	22 (36.7)	7 (11.7)
University of Iowa	Academic, urban, level 1 trauma	Yes	58.1	20 (64.5) 138 (75 - 188) 1.4 (0.8 - 2.0)	24 (77.4) 351 (152 - 663) 4.2 (1.6 - 7.7)	4 (12.9) 3.5 (1.3 - 8.8) 0.04 (0.01 - 0.09)	11 (35.5)	4 (12.9)
WashU in St. Louis	Academic, urban, level 1 trauma	Yes	63.5	43 (82.7) 275 (150 - 500) 3.6 (2.0 - 6.6)	26 (50.0) 201 (105 - 660) 2.4 (1.5 - 8.6)	20 (38.5) 6.0 (2.0 - 8.0) 0.08 (0.02 - 0.10)	9 (17.3)	13 (25.0)

3.2 Objective

To assess the impact of an educational intervention on the delivery of post-intubation sedation in the ED.

3.3 Specific Aims

Aim 1: Evaluate recruitment of mechanically ventilated patients into the ED-SED Pilot.
Hypothesis: On average, 0.3 patients per day will be recruited to participate in the study at each site.
Aim 2: Evaluate the impact of an educational initiative on post-intubation sedation practices in the ED.
Hypothesis 2a: The proportion of RASS scores in the deep sedation range will be reduced by 15% after the educational initiative.
Hypothesis 2b: The interclass correlation coefficient in RASS measurements among bedside nurses will be > 0.90.
Hypothesis 2c: The incidence of adverse events will be similar before and after the educational initiative.
Aim 3: Describe facilitators and barriers to adherence to guideline-supported sedation recommendations with a qualitative assessment of nurses' and physicians' perception and understanding of sedation.

3.4 Endpoints

3.4.1 Primary Endpoints - Feasibility

The primary endpoints to demonstrate feasibility are: 1) participant recruitment; 2) proportion of RASS scores in the deep sedation range; 3) reliability of RASS measurements during routine care in the ED; and 4) adverse events. We will also conduct a qualitative survey of nurses and physicians to better understand facilitators and barriers to adherence to guideline-supported sedation recommendations

3.4.2 Secondary Endpoints – Clinical

3.4.2.1 Clinical Endpoints

The main purpose of the study is to test feasibility and will not be powered to demonstrate efficacy. However, we will also collect clinical outcome data to guide future studies as needed.

1. **Ventilator-free days (VFD) to day 28:** VFD depend on both duration of ventilation and mortality and is typically indexed to study day 28. In participants who survive 28 days, VFD is defined as 28 minus duration of ventilation. Duration of ventilation is counted from the first study day of assisted breathing through the last day of assisted breathing provided the last day is prior to day 28. Otherwise, it is counted from the first study day of assisted breathing through day 28. Isolated periods of ventilation briefer than 24 hours for surgical procedures and ventilation solely for sleep-disordered breathing do not count towards duration of ventilation. Participants who do not survive 28 days will be assigned zero VFD.

2. **ICU- and hospital-free days:** These will be assessed and calculated in a similar fashion as VFD.

3. **Acute brain dysfunction in the ICU:** Acute brain dysfunction is a composite outcome comprised of delirium and coma. Delirium will be assessed by the Confusion Assessment Method for the ICU (CAM-ICU) per standard clinical care. This is a highly reproducible and well-validated method for diagnosing delirium in mechanically ventilated patients. Coma will be defined as having all documented RASS scores of -4 (responsive to only physical stimulus) or -5 (unresponsive) during the first 48 hours. We elect to use this composite outcome since both delirium and coma are major categories of cognitive dysfunction. As delirium cannot be assessed during periods of coma, using this composite outcome provides a more accurate event rate for the incidence of acute organ dysfunction of the brain.

4. **Hospital mortality:** This endpoint is the proportion of participants who have survived at hospital discharge.

4 STUDY POPULATION AND ENROLLMENT

4.1 Number, Source, and Screening

4.1.1 Patient Population

We will screen all consecutive mechanically ventilated ED patients and enroll 400 patients that fulfill inclusion and exclusion criteria.

Recruitment method: All participants for the study will be identified in the ED, and each participating site has standard operating procedures in place to identify consecutive mechanically ventilated patients. Examples include in-person screening by research coordinators in the ED, as well as electronic triggers to capture mechanically ventilated ED patients by identifying the receipt of a neuromuscular blocker (e.g. succinylcholine, rocuronium), mechanical ventilation orders, or an endotracheal intubation procedure note.

Each site will have dedicated study physicians and research assistants who are certified and trained in human subjects protection and understand the study protocol.

4.1.2 Provider Participant Population

We will aim to get survey responses from 150 ED providers (50 physicians and 100 nurses).

Recruitment method: Nurses and physicians will be recruited via electronic mail to participate in the voluntary and anonymous survey to assess facilitators and barriers to adherence to best sedation practices in the ED.

4.2 Inclusion Criteria

1. Age ≥ 18 years
2. Receipt of invasive mechanical ventilation in the ED

4.2.1 Invasive Mechanical Ventilation Initiated in the ED

Patients receiving invasive mechanical ventilation in the ED, per the decision of the treating physician, will be the target population. Mechanical ventilation almost universally requires medication for sedation. Therefore, these patients are the optimal cohort to assess the impact of an educational initiative aimed at improving post-intubation sedation practices, and prior data support the role for targeted sedation in the ED to improve outcome going forward.

4.3 Exclusion Criteria

1. Acute neurologic injury (stroke, intracranial hemorrhage, traumatic brain injury, cardiac arrest, status epilepticus, fulminant hepatic failure)
2. Ongoing neuromuscular blockade
3. Death or transition to comfort measures within 24 hours
4. Transfer to another hospital from the ED
5. Chronic/home mechanical ventilation
6. Transfer directly from the ED to the operating room

4.3.1 Reasons for Exclusions

While guidelines recommend light levels of sedation to improve outcome, deep sedation is warranted in some clinical situations. The exclusion criteria for this study exclude patients in whom: 1) deep sedation could be indicated; and 2) duration of mechanical ventilation is unlikely to be altered by sedation management. It therefore selects for a cohort of patients in whom a sedation protocol which favors light sedation is appropriate as part of standard, routine care. Presence of neurological injury is an exclusion as patients with neurological injury can have depressed levels of consciousness and coma that are independent of sedation, therefore serving as a confounder between sedation depth and clinical outcomes. Patients receiving ongoing neuromuscular blockade have an absolute indication for the receipt of deep sedation, and will therefore be excluded. We exclude patients dying within 24 hours of presentation, because in our experience of conducting studies on mechanically ventilated ED patients, this represents a cohort of patients with an acutely non-survivable illness (e.g. intracranial hemorrhage, refractory shock), or a chronic illness burden prompting next of kin to forego aggressive therapy and opt for early comfort measures. It is therefore unlikely that the sedation approach in the ED would affect outcome. These patients can also be so critically ill that deep sedation is appropriate in their management. Patients that are transferred to another hospital will be excluded, as it would not be possible to obtain clinical data or pertinent outcomes. Patients on chronic/home ventilation typically may require vastly different sedation approaches (i.e. no sedation at all), given their chronic condition. Also, the ability to calculate VFD (a secondary study outcome) in these patients is challenging. Patients that are admitted directly to the operating room from the ED as the sedation provided in the operating room would serve as a confounder in the assessment of pre-ICU care.

4.4 Screening and Study Initiation

All participants will be screened in the ED. All patients satisfying inclusion and exclusion criteria will have pertinent data collection initiated from the patient's ED stay.

4.5 Informed Consent

This study meets the criteria for waiver of informed consent per 45 CFR 46.116.f.3.

(i) The research involves no more than minimal risk to the subjects. The study is entirely observational, and involves no intervention with the subjects. At all times, patients will be cared for at the discretion of the treating clinical team. Specifically, the after phase of the study is focused on

educating staff and reminding them about the existing sedation protocol, with a primary endpoint of seeing if compliance with the protocol improves. The final choice as to how to sedate the patients will remain at the discretion of the treating clinical team at all times. As mentioned above, there is over 20 years of research which supports that best practice for mechanically ventilated patients is the use of goal-oriented sedation protocols which favor light (versus deep) sedation targets when possible. Given these facts, the probability and magnitude of harm associated with this study is not greater than that encountered during routine medical care. The study and data collection will occur remotely via access of the electronic medical record to obtain routine clinical data. Therefore the study will not intervene on routine care in any way or influence care givers by research team presence.

(ii) The research could not practicably be carried out without the requested waiver or alteration. Obtaining consent in the immediate post-intubation period is not feasible, as all patients will be altered and unable to consent in this time period due to medications given to facilitate intubation and sedation, or because of their level of critical illness and commensurate altered mental status. Further, in our experience of conducting research in thousands of mechanically ventilated ED patients, it is rare for a legally authorized representative (LAR) to be present during the post-intubation period in the ED (travel delays, lack of transportation, lack of knowledge regarding patient's presence in the ED). Time-sensitive data capture in the immediate post-intubation period is vital and this research cannot be conducted without these data. Finally, if consent is required then only the subjects who survive, successfully come off the mechanical ventilator, and are neurologically intact will be able to consent. As we are collecting pertinent clinical endpoints in this study, including ventilator-free days, ICU-free days, and mortality, the study would not be able to enroll subjects who have bad outcomes (only good outcomes enrolled), resulting in completely biased data. Thus, it is not practicable to do the study without waiver.

(iii) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format. This does not apply to the current study.

(iv) The waiver or alteration will not adversely affect the rights and welfare of the subjects. See sections "9.1 Potential Risk to Subjects", "9.2 Minimization of Risk", "9.5 Safety Monitoring", and "10.2 Justification of Including Vulnerable Subjects" below, regarding the robust safeguards, precautions, and protections that will be implemented throughout the study.

(v) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation. Given this is an observational study we do not anticipate additional pertinent information for the patients to be identified.

Regarding the qualitative survey of potential barriers to implementation, this aspect of the research proposal meets exemption 45 CFR 46.101(b)(2): Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, and (i) information obtained will be recorded in such a manner that human subjects cannot be identified, directly or through identifiers linked to the subjects, and (ii) any disclosure of the human subjects' responses outside the research will not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

We will use a consent information sheet without signatures as the first page(s) of the survey given to the nurses and physicians who provide care for the participants. We estimate that approximately 300 will respond to the survey.

4.6 Randomization

This is a prospective, observational, before-and-after study, and there will be no randomization process. This is the optimal study design to fulfill the objectives set forth in this study.

4.7 Minorities and Women

No patients will be excluded on the basis of race, ethnicity, or gender. 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% African-American and 10% Hispanic.

5 STUDY PROCEDURES

Trials should be conducted in a setting reflective of good clinical practice that can be clearly described and reproduced in a clinical (non-trial) setting. The standard care elements known to impact outcome in mechanically ventilated patients are already in place at the clinical centers participating in this study. These include quantitative resuscitation for patients with shock and tissue hypoperfusion, early empiric antibiotics and source control in sepsis, lung-protective mechanical ventilation, and aspiration precautions. These elements decrease risk that subjects will vary systematically across the before and after phases of the study and reflect current guideline recommendations. We will monitor the provision and results of key processes of care and pertinent data variables and will implement the sedation protocol efficiently.

5.1 Before Phase Group

Patients in the before phase of the study will receive usual care: clinician-directed sedation after the initiation of mechanical ventilation.

5.2 Protocol Implementation Phase

After 200 patients have been enrolled in the before phase, we will begin an education implementation initiative for three months. In this phase, we will begin quality improvement initiatives to actually implement the existing sedation protocols that are in place at the sites. Implementation will proceed in a similar fashion to how we have successfully implemented other research protocols in the ED, yet be modified to achieve the goals of this study. The educational initiative will include the following: 1) a lecture outlining the background regarding the clinical impact of sedation for mechanically ventilated patients, the importance of sedation protocols on patient outcome, our background data on ED sedation (see section 3.1, Background, above), and an introduction to the ED-SED Pilot study; and 2) a one-page card given to providers, which highlights the rationale of the study and its overarching goals. We will evaluate the use of sedation with a voluntary survey of nurses and physicians in order for us to better understand facilitators and barriers to adherence to guideline-recommended post-intubation care (see Appendix), and to better understand providers' perception of and experience with ED-based sedation protocols. Before every nursing shift in the ED, it is standard practice for the nurses to gather in a "huddle" in order for nursing leadership to provide such things as announcements and reminders. Going forward, as part of this standard nursing huddle, there will be an informal reminder to document sedation depth in all mechanically ventilated patients, as per the existing protocol. Finally, a laminated sedation depth card, which details the elements of sedation depth documentation, will be placed at each nursing station so the nurses do not have to remember the sedation depth elements on their own. The implementation phase is needed because post-intubation sedation is standard care for mechanically ventilated patients at each site, congruent with guideline recommendations. However, our data suggest that these protocols are just not being effectively used in the ED. Implementation will proceed so that targeted sedation is effectively used in the ED as well, allowing us to test the intervention under real-world conditions. 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 (i.e. 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 (Richmond Agitation-Sedation Scale -2 to 0) as the default when possible; and 4) appropriately titrated sedation.

5.3 After Phase Group

Participants in the after phase will also receive standard post-intubation 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 will be emphasized during the education initiative as the most appropriate approach for the majority of patients, they will be treated and sedated as the clinical team deems best and there will be no influence from the study team.

5.3.1 IRB-requested Modification and Further Explanation Regarding the After Phase of the Study

Per the WU IRB minutes (7/1/2020), a modification is requested regarding the after phase of the study.

As a summary, based on over 20 years of research, extensive evidence supports the fact that the best practice for mechanically ventilated patients is the use of sedation protocols for pain and sedation management in critically ill adults. For this reason, post-intubation sedation protocols and order sets have been in place and are part of routine, standard care at each site participating in this study. See section 3.1.1 above ("Background on the three ED-SED Pilot Sites"), along with the accompanying table in that section, to view the historical sedation practices at each site. Additionally, the existing sedation protocols from each site are included in Appendix A of this study protocol. Both our background data and the existing sedation protocols show similarities among the sites with respect to post-intubation sedation for mechanically ventilated patients in the ED. Additionally, interim data from the before phase of the study is shown in the table below.

Table 2. Sedation practices at the ED-SED Pilot sites, before-group data.

Site	Deep sedation incidence, n (%)	Drug n (%) Cumulative dose Weight-based dose		
		Fentanyl	Propofol	Midazolam
Cooper University Hospital	30 (57.7)	49 (94.2) 425 (166 – 913) 3.8 (2.4 – 10.8)	44 (84.6) 360 (191 – 922) 5.0 (2.0 – 11.3)	3 (5.8) 7.0 (5.0 – NA) 0.09 (0.06 – NA)
University of Iowa	34 (85.0)	27 (67.5) 112 (50 - 100) 1.4 (0.8 – 3.3)	32 (80.0) 266 (121 – 626) 3.6 (1.3 – 7.1)	1 (2.5) 5.0 (NA) 0.05 (NA)
WashU in St. Louis	52 (50.0)	92 (88.5) 400 (200 - 788) 5.0 (2.8 - 8.3)	78 (75.0) 444 (187 - 838) 5.4 (2.4 - 10.4)	38 (36.5) 6.5 (3.8 - 10.5) 0.07 (0.04 - 0.15)

These data demonstrate continued similarities among each site- the use of some combination of fentanyl, propofol, and midazolam, via the use of existing sedation protocols and/or order sets in the electronic medical record, to facilitate sedation for mechanically ventilated patients in the ED. It also further demonstrates that post-intubation sedation at each site is standard, and that the current study will not be introducing any new therapy into the routine care of the patients. In the Background (section 3.1), the potential harms associated with deep sedation are demonstrated, and Table 2 above demonstrates a continued high incidence of deep sedation in the before group of this study. This suggests that, despite the existence of ED-based sedation protocols for mechanically ventilated patients, these sedation protocols are not being followed in the ED setting. Therefore, the ED-SED Pilot is needed to assess the impact of an educational initiative aimed at improving sedation practices by improving adherence to guideline-recommended sedation care in the post-intubation period. The study will attempt to optimize (via education) the care that is already in place.

Our intervention is an educational initiative aimed at quality improvement. Please see section 5.2 above, Protocol Implementation Phase, for details regarding the intervention, which will only educate providers on the importance of using the existing sedation protocol effectively. The study will not alter anything about the post-intubation care at a site, and there will be no changes to the standard protocols that are already in place. At all times, clinical care, including all aspects of sedation, will be at the discretion of the treating clinical team and there will be no influence from the study team, nor any study-mandated aspects of care. The study therefore remains completely observational, is minimal risk, and satisfies approval for waiver of the requirement to obtain informed consent as outlined above.

5.4 Common Strategies for Both Groups

This trial will not mandate aspects of routine clinical care because: 1) the intention is to evaluate the protocol in the context of routine clinical care; 2) there is a broad spectrum of conditions leading to the need for mechanical ventilation; 3) the clinical sites already have protocols in place for the standard care elements known to impact prognosis in mechanically ventilated patients; and 4) demonstrating feasibility of the protocol during routine care is a more valid preparation for any future trials that could result from this pilot work.

6 DATA VARIABLES

In-line with the pragmatic nature of the study, patient-level data will be easily accessible from the electronic medical record.

6.1 Background Assessments

1. Inclusion/exclusion criteria
2. Demographic and admission data (including age, gender, race)
3. Pertinent medical history and comorbid conditions [dementia, diabetes mellitus, cirrhosis, congestive heart failure, dialysis/end-stage renal disease, chronic obstructive pulmonary disease, immunosuppression, malignancy, alcohol abuse, psychiatric illness (schizophrenia, bipolar, depression, anxiety)]
4. Height, actual body weight, calculated predicted body weight (PBW), body mass index (BMI)
5. Presenting vital signs
6. Pertinent laboratory values (lactate, creatinine, bilirubin, platelets, arterial blood gas) and illness severity
7. Location of intubation (ED, prehospital, outside hospital/other facility), drugs used to facilitate intubation, and indication for mechanical ventilation
8. Ventilator settings
9. Responses from the modified Brice questionnaire

6.2 ED Process of Care Variables

1. ED length of stay (minutes)
2. Procedures (e.g. central venous catheter, arterial catheter)
3. Antibiotics for infection
4. Blood product transfusion
5. Vasopressor infusion
6. Intravenous fluids

6.3 ED Sedation-Pertinent Variables

1. All medications for ED sedation including: opiates, benzodiazepines, propofol, ketamine, dexmedetomidine, etomidate, haloperidol, quetiapine, and neuromuscular blockers.
2. Sedation depth will be recorded per our standardized order set for post-intubation care, including RASS assessments every hour in the ED.

6.4 Assessments During Hospitalization

We will collect the following in-hospital data by medical record review:

1. Duration of ventilation.
2. Organ failure assessments daily to day 2 (arterial blood gas, bilirubin, creatinine, and vasopressor use), using clinically available data.
3. Agents used for the management of analgesia and sedation during the first 48 hours of ICU admission.
4. Depth of sedation while mechanically ventilated.
5. Acute brain dysfunction (presence of coma and delirium) during the first 7 days of ICU admission.
6. Lengths of stay in the ICU and hospital.
7. Date of hospital discharge or date of death, as applicable.

6.5 Assessments After Hospitalization

Patients will not be followed after discharge from the hospital.

7 STATISTICAL CONSIDERATIONS

7.1 Statistical Methods

The data analyses for this before-after observational study are mostly descriptive. Demographic and treatment variables, as well as participant characteristics, will be summarized by using descriptive statistics such as mean (standard deviation) and median (interquartile range) for continuous variables, and frequency distributions for categorical variables. For recruitment rate and adverse events, the type of data 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 Chi-square test to compare two independent proportions. Logistic regression will be used to compare before-and-after differences, adjusting for potential confounders. For survey results regarding barriers to the implementation, the data will be summarized and reported as frequencies and proportions, and responses from time 1 (before phase) will be compared time 2 (after phase).

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 this pilot proposal demonstrate that 63% of RASS assessments are expected to be in the deep sedation range. We assume an effect size (proportion difference) of 15% (i.e. 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 [1]; 2) feasible to attain; and 3) a clinically meaningful demonstration of adherence to goal-directed sedation. Assuming α=0.05 and power=0.80 (two-tailed), 200 patients will be needed in each phase, i.e. a **total of 400 patients**.

With respect to the analysis of documented adverse events, this study is not powered to detect significant differences in the adverse events between the before and after groups. To analyze adverse events, point and interval estimates of the occurrence of these events in the before and after groups will be presented. As the event rates are expected to be very low (self-extubation <1%, device removal 1-2%) the confidence intervals will be based on the exact binomial method. For completeness in exploratory analyses of these adverse events, Fisher exact test will be used to explore possible significant differences in the occurrence of adverse events between the two groups.

8 DATA COLLECTION AND SITE MONITORING

8.1 Data Collection

Data will be collected from the clinical record and the research staff at each site will record and store data using Research Electronic Data Capture (REDCap), a secure, web-based data management application. Patients will be assigned Study ID numbers, and clinical data will be downloaded and stored according to the Study ID numbers. There will be no protocol-mandated aspects of routine clinical care. For survey questionnaire data collection, respondents will fill out the survey directly into REDCap, completely anonymously. These providers (physicians and nurses in the ED) will be contacted/recruited directly via email, which will provide a link to the REDCap survey.

8.2 Site Monitoring

The PI and study staff will review data on an ongoing basis for completeness and accuracy, as well as protocol compliance. Data quality will also be reviewed with back-end monitoring of data via statistical reports. The overall study PI and site PIs will communicate on an ongoing basis regarding the study.

9 RISK ASSESSMENT

9.1 Potential Risks to Subjects

Data Risks: All data collected as part of this study are part of routine clinical care. There is the slight possibility of unauthorized release of PHI data about participants (i.e. breach of confidentiality). Such disclosure would be extremely unlikely to involve a threat to life, health, or safety but would be an invasion of the participants' privacy. It is conceivable that such disclosure could have psychological, social or legal effects on the participants. The risk of loss of confidentiality is minimized by our standard security procedures. All study personnel who have access to the data will be educated regarding the need to protect confidentiality and the procedure to be followed to ensure such protection. All personnel will complete their own site's university-mandated human subject education program. The computer system on which data are maintained will use standard password protection procedures to limit access to authorized users. The database for this study will be fully HIPAA-compliant. Data to be used for analysis will contain only the assigned identification numbers. The data analysis team will not have access to a master list linking the identification numbers with any normal identifiers such as name, social security number, address and hospital record identification number.

Protocol Risks: Guidelines recommend sedation protocols with target-driven sedation depth goals in mechanically ventilated patients because of a favorable risk-to-benefit ratio, with consistent data showing improved outcomes. While the ED environment is somewhat unique, given the frequency with which mechanical ventilation and sedation is used, there is no empiric reason to believe that adherence to sedation protocols in the ED domain will have a different risk-to-benefit ratio.

Self-extubation/inadvertent extubation is a potential risk of a sedation protocol which favors light sedation. Registry data from the ED demonstrate inadvertent extubation to occur at a rate of 0.30% (*J Emerg Med. 41(4), 347-354*). Our data from the multicenter ED-SED Study showed a self-extubation rate of 0.74% (1 patient lightly sedated and 1 patient deeply sedated). Before-after studies and randomized trials involving sedation protocols (i.e. sedation interruptions, light sedation targets) have consistently shown no difference in the rate of self-extubation associated with light sedation [22].

Device removal (e.g. urinary catheter, venous or arterial access, enteric tubes) is also a potential risk. To our knowledge, this has not been reported in mechanically ventilated ED patients. Data from the ICU demonstrate this incidence to be 1-2% (*Can J Anaesth. 2014; 61(7): 619-630*).

Awareness during mechanical ventilation can lead to serious emotional sequelae. There is a dearth of data on this from the ICU and the ED. As neuromuscular blockers are used to facilitate endotracheal intubation in up to 90% of ED patients, this is an important adverse event to measure. Data from the operating room estimate the incidence of awareness to be <1% (*Anesth Analg. 2004; 99(3): 833-9*). Therefore, in patients that survive and are extubated, we will assess for awareness with the modified Brice questionnaire. Similar to how we have assessed for awareness in a prior study (IRB ID# 201905074), we will also conduct this portion of the study with waiver of informed consent for the following reasons: 1) assessing awareness after extubation is part of routine post-intubation care for the millions of mechanically ventilated patients undergoing anesthesia annually in the U.S., and should be routine in all care domains; 2) obtaining informed consent immediately after intubation would render this portion of the study not feasible; 3) time-sensitive data capture in the immediate post-intubation period is vital and this research cannot be conducted without these data; 4) all eligible patients are needed to avoid biasing the data; and 5) we already have robust safeguards in our network to ensure data confidentiality.

Standard treatment risk: The current conventional approach to post-intubation sedation in the ED involves a high incidence of deep sedation, which we have shown to increase the incidence of deep sedation in the ICU [24,25]. Furthermore, we have shown that deep sedation in the ED is negatively associated with clinical outcomes, including ventilator duration, lengths of stay, mortality, and acute brain dysfunction [24,25]. This suggests that currently, despite our ED-based publications and existing treatment guidelines regarding post-intubation sedation, clinicians are not targeting (or perhaps not paying attention to) sedation in post-intubation care. Therefore, we contend that the current approach to sedation in the ED is a greater threat to patient safety than the quality improvement intervention we propose.

Questionnaire Administration Risks: The qualitative survey of nurses and physicians is designed to assess potential barriers to implementing an ED-based sedation protocol. This is an important aspect of effectively implementing a sedation protocol that is geared toward improving care delivery and patient outcome, but is also embraced by bedside nurses and treating physicians. Although unlikely, as a consequence of questionnaire completion, participants may experience emotional discomfort. If any particular question makes a participant feel uncomfortable, he or she may choose not to answer it. In addition, completion of the questionnaire is voluntary and completely anonymous. The participant's choice will not at any time affect any aspect of their job, clinical environment, or patient care.

Awareness Questionnaire Administration Risks: Although unlikely as a consequence of completing the questionnaire, patients may experience emotional discomfort. If any particular question makes a participant feel uncomfortable, he or she may choose not to answer it. In addition, completion of the questionnaire is voluntary. The participant's choice will not at any time affect any aspect of their care. Assessment of awareness with recall is part of routine post-extubation care annually for millions of OR patients. Based on the complications associated with awareness, we believe assessing for awareness carries a favorable risk-to-benefit ratio. If awareness is identified, the treating clinical team will be notified and the patient will be offered counseling.

9.2 Minimization of Risk

All clinical care will be performed in state-of-the-art medical facilities at the study sites. The risks above are rare and are further minimized by the fact that they are limited to patients who already require mechanical ventilation and sedation. Further, our inclusion and exclusion criteria select for patients in whom targeted sedation is appropriate (i.e. deep sedation not clinically indicated). At all times, treating clinicians will manage patients with the primary interest of patient care first. All research staff personnel involved in this proposal have undergone training in Good Clinical Practice guidelines for research studies. Any risk to confidentiality for participants is low. All key personnel involved in the design or conduct of research involving human subjects have obtained required education on protection of human research participants prior to funding of this project.

General data precautions and safeguards: The study leadership is sensitive to needs for data security, including that related to PHI, and the study staff is experienced in the operation of databases and in protecting them against loss or misuse. We will hold periodic staff meetings to remind personnel of required operating procedures and safeguards and monitor adherence to precautions and safeguards. We will ensure that all staff have appropriate training to comply with their medical center's policies and procedures related to the HIPAA. Only study investigators will have access to individually identifiable patient information, and clinical data will be de-identified as soon as possible.

Patient confidentiality safeguards: We will ensure that all data flow procedures from the study sites exclude the transmission of patient identifying information. For example, data will be uploaded from each site into REDCap, and no patient identifiers will be included in this master dataset. Patient identifying information will be stored at each site electronically in an encrypted form or in a separate file, on password-protected research computers.

Safeguards against misuse of data: We will limit the number of persons who have access to any study data, especially those containing patient identifying information. Patients will be assigned Study ID numbers, and clinical data will be stored according to the Study ID numbers. A master list pairing patients to the Study IDs will be kept on a password-protected file on a password-protected computer. Password-restricted access to data files containing study results will improve security. Separate passwords for files, server, and computer desktops, frequent change of passwords, and use of password-choice guidelines requiring alpha-numeric passwords will all improve data security. All materials will be stored in a secured environment. Data will be encrypted, managed in REDCap, and password-protected.

Data loss safeguards: All data entered into the REDCap database will be stored on Washington University servers. Thus, all project data is stored and hosted at the local institution, and no project data is ever transmitted at any time by REDCap from Washington University to another institution or organization. User privileges related to data management (i.e. beyond that related to data entry) will be restricted to site PIs. As a standard operating procedure, the use of REDCap to enter and store data prior to analysis, in a secure and password-protected manner provides certainty that data will not be lost.

Data security and confidentiality: After study completion, data will be exported into a statistical analysis package (e.g. SAS) for analysis by our biostatistician (Yan Yan, PhD), who is a member of the Division of Biostatistics at Washington University. No PHI will be exported and analysis will proceed in a way such that patient confidentiality is completely maintained. Standard procedures provide substantial certainty that data stored within the Division of Biostatistics will never be lost and that confidentiality will be maintained. Longstanding Division policies emphasizing these issues include requiring that employees sign confidentiality agreements, that personal identifiers are included in electronic databases only under strong necessity, that encryption be used when identifiers are present, that access to data is password protected, and that all data are backed up in accordance with standard operating procedures. Access to all systems in the Division is restricted to Division faculty, staff, and collaborators. Access to study data will be restricted to study personnel. The entire Division of Biostatistics network wiring plant is behind a firewall and access to all computers is logged. Finally, should problems arise with the system, a full-time network engineer runs the system and is on call (with backup) 24 hours a day, 7 days a week.

Data and database safeguards: Data will be stored according to HIPAA compliance regulations and the policies of the NIH and local IRBs. PHI will not be stored on media accessible from external locations. Computer and storage disks will have password protection. Data files will be stored in locked cabinets in locked rooms.

Protocol-Related Protection: A sedation protocol in the immediate post-intubation period carries minimal risk. Sedation protocols that target a specific sedation depth and monitor depth of sedation are standard care for mechanically ventilated patients and already in place for use in the ED. This study aims to codify and make more precise an initiative that should be executed better and is of great interest to practicing clinicians. Over 20 years of research which supports the fact that best practice for mechanically ventilated patients is the use of goal-oriented sedation protocols which favor light (versus deep) sedation targets when possible. Regarding potential risks associated with sedation in the ED, as detailed above, these risks are extremely rare and have not been associated with the use of sedation protocols in other domains. Given these facts, the probability and magnitude of harm associated with this study is not greater than that encountered during routine medical care. However, we will monitor adverse events across the duration of the study. In addition, our inclusion and exclusion criteria select for a population in which targeted sedation is safe and clinically indicated. For example, patients receiving ongoing neuromuscular blockade will not be included in the study because they have an absolute indication to have very deep sedation.

Questionnaire-Related Protection: The sedation knowledge and impediment survey will be designed and managed in REDCap. Respondents will upload their responses directly into REDCap, with no identifying information included. Completion of the questionnaire is completely voluntary and completely anonymous. The awareness questionnaire will also be managed in REDCap. Responses will be uploaded directly into REDCap. No identifying information will be exported from the database.

9.3 Potential Benefits

Based on our preliminary data, we can say that a goal-oriented sedation protocol implemented in the ED has the potential to improve the morbidity and mortality associated with acute respiratory failure requiring mechanical ventilation. There is also great potential for indirect benefit with participation in this study. From a societal standpoint, we will have a greater understanding of a therapy shown to have short- and long-term benefit when studied in the ICU. The primary purpose of this pilot study is to examine the feasibility of implementing an ED-based, goal-oriented, sedation protocol for mechanically ventilated patients. As such, it is not powered to examine efficacy with respect to clinical endpoints, but to assess feasibility and assist in planning and refinement of any future clinical trials. As such, completion of this project will benefit those enrolled in future investigations.

9.4 Risks in Relation to Anticipated Benefit

Federal regulations require that the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. Given the procedures to minimize risks and protect privacy in this study, the low risk nature of the research, and the potential benefits to study participants as well as future patients, we believe that the risk/benefit ratio is favorable for participation in this study.

9.5 Safety Monitoring

The PI together with the study team and the DSMB will review all study data, including all adverse events, compliance with IRB requirements, investigator compliance, minimizing risks and protecting the confidentiality

of participant data. An institutional DSMB at Washington University in St. Louis will be used for this study. It will consist of a small group of experts independent of the study, including a biostatistician, emergency physician, and pulmonary/critical care physician. DSMB members will familiarize themselves with the protocol and communicate by email and regularly scheduled meetings. They will periodically review the developing data related to implementation of the protocol, as well as outcome and safety data.

As this is a preparatory pilot trial aimed at assessing the impact of an educational initiative on post-intubation sedation in the ED, it will not be powered to detect a statistical difference in clinical endpoints or adverse events. Therefore a key role of the DSMB will be in evaluating successful enrollment and implementation of the protocol. They will accomplish this by reviewing data on such aspects as participant enrollment, study procedures, efficacy in achieving target sedation, reliability of sedation measurements during routine care in the ED, data quality, losses to follow up, and other measures of adherence to the protocol.

While the study is not anticipated to be able to detect differences in adverse events, another key role of the DSMB will be to review any adverse events that occur during the study. All adverse events determined to be related to the study and unanticipated problems involving risks to subjects or others will be reviewed by the study team and reported to the IRB at Washington University and the NHLBI according to stipulations.

The PI and the study team will prepare summary reports for the DSMB at the end of the before phase. During the after phase, the DSMB will review the prepared study data for safety every month.

The prepared data and safety monitoring report for each formal DSMB meeting, will include the following items: number of potential participants eligible, number of eligible participants enrolled, protocol implementation data (depth of sedation, RASS measurements, sedative drugs), adverse events, unforeseeable outcomes, clinical outcomes (delirium, coma, lengths of stay, ventilator duration, death), and a statistical comparison of rates of events between the study groups. Data will be presented in a blinded manner during the open sessions of the DSMB. At DSMB meetings, data and discussion will be confidential. DSMB members will not know study participant identities.

10 HUMAN SUBJECTS

Institutional review board approval will be required before any subject is entered into the study. The study will use a central IRB at Washington University in St. Louis.

10.1 Selection of Subjects

This study will identify patients presenting to the ED requiring mechanical ventilation in three academic centers (Washington University, University of Iowa, and Cooper University Hospital). Patients satisfying inclusion and exclusion criteria will be enrolled and data collection will begin in the ED. Study exclusion criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals from participation in the research. Hence, the recruitment of subjects conforms to the principle of distributive justice.

10.2 Justification of Including Vulnerable Subjects

All patients will be those that are mechanically ventilated in the ED. While this patient population has impaired decision-making capabilities, this trial will test the implementation under routine care, in accordance with guideline recommendations regarding sedation for mechanically ventilated patients. As such, participation in this study will not affect the care of the individual. Further, as all patients will already be on a mechanical ventilator as the primary inclusion criteria, those recruited for this trial are not being unfairly burdened with involvement in this research simply because they are easily available.

10.3 Informed Consent

This study meets the criteria for waiver of informed consent per 45 CFR 46.116.f.3.

(i) The research involves no more than minimal risk to the subjects. The study is entirely observational, and involves no intervention with the subjects. At all times, patients will be cared for at the discretion of the treating clinical team. Specifically, the after phase of the study is focused on educating staff and reminding them about the existing sedation protocol, with a primary endpoint of seeing if compliance with the protocol improves. The final choice to follow the protocol will remain at the discretion of the treating clinical team at all times. As mentioned above, there is over 20 years of research which supports that best practice for mechanically ventilated patients is the use of goal-oriented sedation protocols which favor light (versus deep) sedation targets when possible. Given these facts, the probability and magnitude of harm associated with this study is not greater than that encountered during routine medical care. The study and data collection will occur remotely via access of the electronic medical record to obtain routine clinical data. Therefore the study will not intervene on routine care in any way or influence care givers by research team presence.

(ii) The research could not practicably be carried out without the requested waiver or alteration. Obtaining consent in the immediate post-intubation period is not feasible, as all patients will be altered and unable to consent in this time period due to medications given to facilitate intubation and sedation, or because of their level of critical illness and commensurate altered mental status. Further, in our experience of conducting research in thousands of mechanically ventilated ED patients, it is rare for a legally authorized representative (LAR) to be present during the post-intubation period in the ED (travel delays, lack of transportation, lack of knowledge regarding patient's presence in the ED). Time-sensitive data capture in the immediate post-intubation period is vital and this research cannot be conducted without these data. Finally, if consent is required then only the subjects who survive, successfully come off the mechanical ventilator, and are neurologically intact will be able to consent. As we are collecting pertinent clinical endpoints in this study, including ventilator-free days, ICU-free days, and mortality, the study would not be able to enroll subjects who have bad outcomes (only good outcomes enrolled), resulting in completely biased data. Thus, it is not practicable to do the study without waiver.

(iii) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format. This does not apply to the current study.

(iv) The waiver or alteration will not adversely affect the rights and welfare of the subjects. See sections "9.1 Potential Risk to Subjects", "9.2 Minimization of Risk", "9.5 Safety Monitoring", and "10.2 Justification of Including Vulnerable Subjects" below, regarding the robust safeguards, precautions, and protections that will be implemented throughout the study.

(v) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation. Given this is an observational study we do not anticipate additional pertinent information for the patients to be identified.

Regarding the qualitative survey of potential barriers to implementation, this aspect of the research proposal meets exemption 45 CFR 46.101(b)(2): Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, and (i) information obtained will be recorded in such a manner that human subjects cannot be identified, directly or through identifiers linked to the subjects, and (ii) any disclosure of the human subjects' responses outside the

research will not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

We will use a consent information sheet without signatures as the first page(s) of the survey given to the nurses and physicians who provide care for the participants.

10.4 Confidentiality

See “Minimization of Risk” above.

11 ADVERSE EVENTS

11.1 Safety Monitoring

Assuring patient safety is an essential component of this protocol. Each participating investigator has primary responsibility for the safety of the individual participants under his or her care. Safety data including Adverse Events (AE) and Serious Adverse Events (SAE) will be presented according to study group at each DSMB meeting. The investigators and their IRBs have established policies and procedures to identify, report, and review adverse events.

An AE is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered an investigational product and that does not necessarily have a causal relationship with this product. An AE can therefore be any unfavorable and unintended sign such as an abnormal laboratory finding, symptom, or disease temporarily associated with the use of an investigational product, whether or not considered related. An SAE is defined as any untoward medical occurrence that results in death, is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is an important medical event based upon appropriate medical and scientific judgment, results in potential drug induced liver injury, or results in suspected transmission of an infectious agent via the study drug.

The DSMB physicians, independent of the study team, will grade the causal relationship to the study. The AE attribution scale can be one of the following:

a. Definitely related: AE is clearly related to the investigational agent/procedure/ intervention.
b. Probably related: AE is likely related to the investigational agent/procedure/ intervention.
c. Possibly related: AE is possibly related to the investigational agent/procedure/ intervention.
d. Unlikely related: AE is doubtfully related to the investigational agent/procedure/ intervention.
e. Unrelated: AE is clearly not related to the investigational agent/procedure/ intervention.

Classification of AE severity: AEs will be labeled according to severity, which is based on their impact on the patient. An AE will be termed “mild” if it does not have a major impact on the patient, “moderate” if it causes the patient minor inconvenience, and “severe” if it causes a substantial disruption to the patient’s well-being.

AE Reporting and Follow Up: Adverse events will be summarized in table format with information including Study ID number, date of AE, description of event, severity classification, designation as serious or not, attribution, action taken, and outcomes.

SAE Reporting: SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the DSMB and the IRB. Unexpected, life-threatening AEs related to the intervention will be reported

within 7 days. Other serious and unexpected AEs related to the intervention will be reported within 15 days. Anticipated or unrelated SAEs will be reported in a less urgent manner but within accordance of IRB requirements. In the annual AE summary, the DSMB will state that they have reviewed all AE reports.

APPENDICES

A. Sedation Protocols

A1. Washington University

ED TCC Unit Sedation Orders for Mechanically Ventilated Patients	ADDRESSOGRAPH

UNLESS THE WORD SPECIFIC IS WRITTEN AFTER A DRUG ORDER BY TRADE NAME, A GENERIC EQUIVALENT DRUG APPROVED BY THE PHARMACY AND THERAPEUTICS COMMITTEE MAY BE DISPENSED IN ACCORDANCE WITH THE MEDICAL STAFF BYLAWS.

Please check (4) the appropriate box □ and fill in the blank(s) as needed. IF you do not need an order, draw a line through it and initial.

DATE	TIME	ORDERS
		Before initiating sedation orders, assess the indication(s) for sedation.
		□ Target RASS 0 to -2 □ Other RASS goal: □ -3 □ -4 □ -5
		Analgesia Initiation and Breakthrough: □ Fentanyl _____ mcg (typical starting dose 25-100 mcg) IVP PRN Q5 minutes (Max dose 300 mg in 15 minutes). MAR Entries 6. Reason: Pain **Sedation Initiation and Breakthrough:** □ Propofol _____ mg IVP (typical starting dose 0.5mg/kg, Max single bolus = 50mg). Now. MAR Entries 1. Reason Sedation. □ Midazolam _____ mg (typical starting dose 1-5 mg) IVP PRN Q5 minutes (**Max dose 15 mg in 15 minutes**). MAR Entries 6. Reason: Sedation
		Analgesia Maintenance: □ Fentanyl infusion _____ mcg/hour (typical starting dose 50 mcg/hour. **Max dose 200 mcg/hour; higher doses require MD order**). Reason: Pain **Sedation Maintenance:** Choose one: □ Midazolam infusion at _____mg/hour (typical starting dose 1-2 mg/hr. (**Max dose 8 mg/hour; higher doses require MD order**). Titrate to target RASS goal. Reason: Sedation. □ Propofol _____ mcg/kg/minute (typical starting dose 10-25 mcg/kg/minute), increase rate 10 mcg/kg/min PRN Q5 minutes (**Max dose 50 mcg/kg/min, higher doses require MD order**). Titrate to target RASS goal. Reason: Sedation.
		Sedation Monitoring and Dose Titration **Sedation is:** **ADEQUATE (RASS at specified goal) if < 2 PRN doses given in previous 2 hours** 1. Continue current medication(s), dosage and Q1 hour monitoring **UNDERSEDATED (RASS +1 above specified goal) if ≥ 2 PRN doses given in previous 2 hours.** **Increase sedation/analgesia as follows and <u>reassess Q1 hour:</u>** 1. Repeat Sedation/Analgesia initiation to achieve desired sedation level 2. Increase midazolam by 1 mg/hr or propofol by 10 mcg/kg/minute 3. Increase fentanyl by 25 mcg/hr **OVERSEDATED (RASS -1 below specified goal)** **Decrease sedation/analgesia as follows and <u>reassess Q1 hour:</u>** 1. Decrease midazolam infusion by ½ of infusion rate (or discontinue if less than 1 mg/hour) 2. Decrease propofol infusion by 10 mcg/kg/minute (or discontinue if less than 10 mcg/kg/minute) 3. Decrease fentanyl infusion by ½ of infusion rate (or discontinue if less than 25 mcg/hour)
		Discontinue all induction, PRN and maintenance sedation/analgesia upon extubation
		Physician:_____ _____ **Telephone#/Pager#_____**

A2. Cooper University Hospital

Cooper University Health Care

Pain, Agitation, Delirium Protocol, for Mechanically Ventilated Adult Patients

Establish Target Pain & Sedation Scores

Pain: Assess and document level of pain **every 1 hour** and as needed. For pain score 4-10.

Agitation: Assess and document level of sedation **every 1 hour** and as needed using the Richmond Agitation Sedation Scale. Goal RASS {-1 to +1}.

Delirium: Assess and document presence of delirium using the Confusion Assessment Method for the Intensive Care Unit (**CAM-ICU**) **every shift** (and during daily interruption of sedation) and PRN. *NOTIFY PHYSICIAN IMMEDIATELY IF DELIRIUM IS PRESENT.*

Spontaneous breathing trial every 24 hours only if clinically appropriate: (ICU Patients only: If patient fails spontaneous breathing trial, re-initiate sedative and pain medications at half the previous dose).

***Note:** For any step, medications ordered may differ from those included on this protocol. Contact provider with any questions/concerns before administering*

PAIN MANAGEMENT

STEP 1 Induction (For pain score 4 – 10) First 24 hours post intubation only

Fentanyl injection See order	OR	HYDROmorphone injection See order

STEP 2 Maintenance—Intermittent Bolus Dosing (For pain score 4 – 10)

Fentanyl injection See order	OR	HYDROmorphone injection See order

STEP 3 Maintenance—Continuous Infusion (For pain score 4 – 10)

Initiate continuous infusion if the patient requires all three pain induction doses **OR** *if the patient's pain is uncontrolled with intermittent bolus dosing of an opiate*

Fentanyl infusion *Notify physician upon infusion initiation and if dose required exceeds dose range in order* ***For pain score 4-10, administer linked bolus order and increase rate of infusion per order**	OR	HYDROmorphone infusion *Notify physician upon infusion initiation and if dose required exceeds dose range in order* ***For Pain score 4-10, administer linked bolus order and increase rate of infusion per order**

Pain score 4 - 10 & RASS above goal	Pain score 4 - 10 & RASS below goal	Pain score 0 - 3 & RASS above goal	Pain score 0 - 3 & RASS below goal
• Treat pain first • Refer to Step 2 & 3	• Contact provider for further instructions	• Treat agitation with sedative • Refer to Step 4 & 5	• Decrease sedative by 50% first. If Pain score & RASS remain below goal in 1 hour, decrease opioid dose by 50%.

AGITATION MANAGEMENT *Must treat pain first*

STEP 4 Induction (For Initial RASS score of +3 to +4)

Midazolam injection See order	OR	Lorazepam injection See order

STEP 5 Agitation Management (For RASS score of >1)

Propofol infusion *(Review every 24hrs)* *Notify physician upon infusion initiation and if dose required exceeds dose range in order* ***After 72hrs of continuous Propofol infusion order Triglycerides with am labs***	Dexmedetomidine infusion *(Review every 24hrs)* *Notify physician upon infusion initiation and if dose required exceeds dose range in order*

A3. University of Iowa

Adult Intubation and Mechanical Ventilation Order Set

DATE	TIME	ORDERS
		INTUBATION
		Paralytics: □ Succinylcholine ____mg (1.0-1.5 mg/kg), Intravenous, Once □ Rocuronium ___mg (1.0-1.2 mg/kg), Intravenous, Once
		Induction Agents: □ Etomidate (AMIDATE) ___mg (0.3 mg/kg), Intravenous, Once □ Midazolam (VERSED) ___mg (0.1 mg/kg), Intravenous, Once □ Ketamine (KETALAR) ___mg □ Propofol (DIPRIVAN) ___mg
		POST-INTUBATION ANALGESIA AND SEDATION
		□ Fentanyl injection, ___mcg (25-100 mcg), Intravenous, PRN Q15 minutes □ Midazolam injection, ___ mg (1-5 mg), Intravenous, PRN Q15 minutes □ Propofol injection, ___ mg (0.5 mg/kg), Intravenous, Once □ Propofol infusion, ___ mcg/kg/min (10-50 mcg/kg/min), Intravenous

B. Time-Events Schedule

Measurement/Event	0*	1	2	3	4	5	6	7	MV**	HOSP D/C
Inclusion/exclusion criteria	X									
Demographics	X									
Co-morbid conditions	X									
Height, weight, PBW, BMI	X									
Vital signs and pertinent labs	X									
Illness severity- SOFA	X									
Intubation details	X									
Ventilator settings/data	X									
ED process of care variables	X									
Medications for sedation	X	X	X							
RASS measurements	X	X	X						X	
Incidence of deep sedation	X	X	X						X	
Organ failure assessment	X	X	X							
Delirium assessment, CAM-ICU	X	X	X	X	X	X	X	X		
Ventilator status	X									X
Length of stay (hospital and healthcare facility)										X
Mortality status										X

* Day 0 refers to the emergency department

** MV refers to the entire period of mechanical ventilation

C. Modified SOFA Scoring System

SOFA Score	0	1	2	3	4
Respiration[A] PaO_2/F_IO_2 (mm Hg) or imputed P/F using SaO_2/F_IO_2	≥400	<400	<300	<200	<100
Coagulation Platelets $10^3/mm^3$	≥150	<150	<100	<50	<20
Liver Bilirubin (mg/dL)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular[B] Hypotension	No hypotension	MAP <70	Dopamine ≤ 5 or dobutamine (any)	Dopamine >5 or norepinephrine ≤ 0.1 or epinephrine ≤0.1	Dopamine >15 or norepinephrine >0.1 or epinephrine >0.1
Renal Creatinine (mg/dL) or urine output (mL/d)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500 mL/day	>5.0 or <200 mL/day

A: Values for scores 3 and 4 are with respiratory support

B: Adrenergic agents administered for at least one hour (doses given in µg/kg/min)

D. De-identified data elements for screened, non-enrolled

Data elements will be collected on screened subjects that are not enrolled, including reason (s) patient excluded from study:

1. Acute neurologic injury (stroke, intracranial hemorrhage, traumatic brain injury, cardiac arrest, status epilepticus, fulminant hepatic failure).
2. Ongoing neuromuscular blockade.
3. Death or transition to comfort measures within 24 hours.
4. Transfer to another hospital from the ED
5. Chronic/home mechanical ventilation
6. Transfer directly from the ED to the operating room

E. Definitions of pre-existing comorbid conditions

Dementia: documentation of clinical history in patient's medical record, including all types of dementia (e.g. Alzheimer's, vascular, Lewy body, Parkinson's, etc.)

Diabetes Mellitus: Documentation of clinical history in patient's medical record; current presentation congruent with diabetes mellitus (e.g. diabetic ketoacidosis).

Cirrhosis: Biopsy proven cirrhosis or medical record history suggestive of cirrhosis (ascites, coagulopathy, nodular liver on computed tomography scan or ultrasound).

Heart failure: Clinical diagnosis on current presentation or history of heart failure in the medical record; includes systolic and diastolic heart failure.

Dialysis/end stage renal disease: Current use of peritoneal dialysis or hemodialysis as an outpatient.

COPD: Not fully reversible airflow limitation; FEV1 <80% + FEV1/FVC <70%; history of COPD in patient's medical record.

Immunosuppression: Therapy with immunosuppressants, chemotherapy, radiation, long term/recent high dose steroids, active leukemia, lymphoma, or acquired immunodeficiency syndrome (AIDS).

Malignancy: Documentation of current or clinical history of malignancy in patient's medical record; includes all solid malignancies (e.g. carcinoma, sarcoma, central nervous system cancers), leukemia, lymphoma, or myeloma

Alcohol abuse: Known diagnosis of chronic alcoholism; previous admission for alcohol detoxification or withdrawal; daily consumption of >14 drinks/week or > 5 binges.

Psychiatric illness: History schizophrenia, bipolar, depression, or anxiety

F. Emergency Department Sedation Protocol Survey

Based on our prior research regarding Emergency Department sedation, we believe that by improving the process of sedation for mechanically ventilated patients, we can improve outcome. For research purposes, you are being asked to fill out this survey in order for us to assess the potential barriers and facilitators to the routine adoption of a goal-oriented sedation protocol in the ED.

Your Privacy is Protected. The research team will not record any information that would let someone identify you. The research team will not have access to any of your personal information. Your responses to this survey are also completely confidential and will not be shared with anybody.

Your Participation is Voluntary. You may choose to answer this survey or not. If you choose not to, this will not affect you in any way.

For each item below, please indicate how strongly you agree or disagree with the statement.

- Disagree strongly
- Disagree somewhat
- Neutral
- Agree somewhat
- Agree strongly

1. I believe sedation for mechanically ventilated patients is a common situation frequently experienced by patients in my ED.
2. I believe sedation for mechanically ventilated patients is managed well in my ED.
3. I believe a sedation protocol is being consistently used in my ED.
4. I believe goal-oriented sedation depth, targeting a specific RASS, is important for patient outcome.
5. I am confident in my ability to use the RASS to assess depth of sedation.
6. I understand the components of the RASS.

7. I believe assessing depth of sedation with the RASS is too time consuming.
8. I believe the documentation involved in the RASS is too time consuming.
9. I believe deep sedation negatively effects patient outcomes in my ED.
10. I believe the physician's role is the most important when achieving on-target sedation depth.
11. I believe the nurse's role is the most important when achieving on-target sedation depth.
12. I prefer patients to be deeply sedated (unresponsive).
13. I prefer patients to be lightly sedated (calm and interactive).
14. I have the support I need from other personnel to use a sedation protocol in mechanically ventilated patients.
15. In my ED, it is difficult to speak up if I perceive a problem with patient care.
16. Management/leadership supports my efforts to manage critically ill patients in my ED.
17. Disagreements in my ED are resolved appropriately.
18. It is easy for personnel in my ED to ask questions when there is something that they do not understand.
19. The physicians and nurses in my ED work together as a well-coordinated team.
20. The levels of staffing in my ED are sufficient to handle the management of mechanically ventilated patients.
21. I experience good collaboration with nurses in my ED.
22. I experience good collaboration with physicians in my ED.
23. Communication breakdowns that lead to delays in delivery of care are common in my ED.
24. I regularly provide input during the ED stay for mechanically ventilated patients.
25. My input is well received in my ED.

For each item below, please indicate your answer and/or provide free text answers to better address the item.

1. The part of the sedation protocol that is most beneficial to patients is: 1) addressing pain in all patients; 2) having a coordinated care plan with respect to sedation; 3) having a goal-oriented RASS target for sedation depth; 4) targeting light sedation; 5) other, please specify _____

2. The part of the sedation protocol that is least beneficial to patients is: 1) addressing pain in all patients; 2) having a coordinated care plan with respect to sedation; 3) having a goal-oriented RASS target for sedation depth; 4) targeting light sedation; 5) other, please specify _____

3. My biggest challenge in implementing a sedation protocol is _____

4. My biggest concern in implementing a sedation protocol is _____

5. The best way to improve the sedation protocol in our ED would be _____

6. I learned the most about the sedation protocol by: 1) completing the on-line educational program; 2) attending in-services; 3) graphics displayed in my clinical area; 4) pocket cards; 5) informal bedside education from the study team; 6) other, please describe_____

G. References

1. Shehabi Y, Bellomo R, Reade MC, et al. Early goal-directed sedation versus standard sedation in mechanically ventilated critically ill patients: a pilot study. *Critical care medicine.* 2013;41(8):1983-1991.
2. Easter BD, Fischer C, Fisher J. The use of mechanical ventilation in the ED. *The American journal of emergency medicine.* 2012;30(7):1183-1188.
3. Fuller BM, Ferguson IT, Mohr NM, et al. Lung-Protective Ventilation Initiated in the Emergency Department (LOV-ED): A Quasi-Experimental, Before-After Trial. *Annals of Emergency Medicine.* 2017.
4. Fuller BM, Mohr NM, Dettmer M, et al. Mechanical ventilation and acute lung injury in emergency department patients with severe sepsis and septic shock: an observational study. *Academic Emergency Medicine.* 2013;20(7):659-669. PMCID: PMC3718493.
5. Fuller BM, Mohr NM, Miller CN, et al. Mechanical Ventilation and ARDS in the ED: A Multicenter, Observational, Prospective, Cross-sectional Study. *Chest.* 2015;148(2):365-374. PMCID: PMC4524326.
6. Page DB, Drewry AM, Ablordeppey E, Mohr NM, Kollef MH, Fuller BM. Thirty-day hospital readmissions among mechanically ventilated emergency department patients. *Emergency Medicine Journal.* 2018.
7. Burns SM, Earven S, Fisher C, et al. Implementation of an institutional program to improve clinical and financial outcomes of mechanically ventilated patients: one-year outcomes and lessons learned. *Critical care medicine.* 2003;31(12):2752-2763.
8. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous iv sedation is associated with prolongation of mechanical ventilation. *Chest.* 1998;114(2):541-548.
9. Arabi Y, Haddad S, Hawes R, et al. Changing sedation practices in the intensive care unit--protocol implementation, multifaceted multidisciplinary approach and teamwork. *Middle East journal of anaesthesiology.* 2007;19(2):429-447.
10. Brattebø G, Hofoss D, Flaatten H, Muri AK, Gjerde S, Plsek PE. Effect of a scoring system and protocol for sedation on duration of patients' need for ventilator support in a surgical intensive care unit. *Bmj.* 2002;324(7350):1386-1389.
11. Brook AD, Ahrens TS, Schaiff R, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Critical care medicine.* 1999;27(12):2609-2615.
12. Chanques G, Jaber S, Barbotte E, et al. Impact of systematic evaluation of pain and agitation in an intensive care unit. *Critical care medicine.* 2006;34(6):1691-1699.
13. De Jonghe B, Bastuji-Garin S, Fangio P, et al. Sedation algorithm in critically ill patients without acute brain injury. *Critical care medicine.* 2005;33(1):120-127.
14. Devlin JW, Holbrook AM, Fuller HD. The effect of ICU sedation guidelines and pharmacist interventions on clinical outcomes and drug cost. *Annals of Pharmacotherapy.* 1997;31(6):689-695.
15. Jakob SM, Lubszky S, Friolet R, Rothen HU, Kolarova A, Takala J. Sedation and weaning from mechanical ventilation: effects of process optimization outside a clinical trial. *Journal of critical care.* 2007;22(3):219-228.
16. MacLaren R, Plamondon JM, Ramsay KB, Rocker GM, Patrick WD, Hall RI. A prospective evaluation of empiric versus protocol-based sedation and analgesia. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy.* 2000;20(6):662-672.
17. Marshall J, Finn CA, Theodore AC. Impact of a clinical pharmacist-enforced intensive care unit sedation protocol on duration of mechanical ventilation and hospital stay. *Critical care medicine.* 2008;36(2):427-433.
18. Mascia MF, Koch M, Medicis JJ. Pharmacoeconomic impact of rational use guidelines on the provision of analgesia, sedation, and neuromuscular blockade in critical care. *Critical care medicine.* 2000;28(7):2300-2306.
19. Quenot J-P, Ladoire S, Devoucoux F, et al. Effect of a nurse-implemented sedation protocol on the incidence of ventilator-associated pneumonia. *Critical care medicine.* 2007;35(9):2031-2036.
20. Tierney M, Snell CC, Cardinal P, Baxter A. Comparison of duration of mechanical ventilation and cost associated with midazolam and lorazepam infusions in critically ill patients. *The Canadian Journal of Hospital Pharmacy.* 1996;49(4).

21. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Critical Care Medicine.* 2018;46(9):e825-e873.

22. Jackson DL, Proudfoot CW, Cann KF, Walsh T. A systematic review of the impact of sedation practice in the ICU on resource use, costs and patient safety. *Critical Care.* 2010;14(2):1.

23. Stephens RJ, Dettmer MR, Roberts BW, et al. Practice Patterns and Outcomes Associated With Early Sedation Depth in Mechanically Ventilated Patients: A Systematic Review and Meta-Analysis. *Critical Care Medicine.* 2017;46 (3):471-479. PMCID: PMC5825247.

24. Stephens RJ, Ablordeppey E, Drewry AM, 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):963-971. PMCID: PMC5812748.

25. Fuller BM, Roberts BW, Mohr NM, 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. *Critical Care Medicine.* 2019.

26. Payen J-F, Chanques G, Mantz J, et al. Current Practices in Sedation and Analgesia for Mechanically Ventilated Critically Ill PatientsA Prospective Multicenter Patient-based Study. *The Journal of the American Society of Anesthesiologists.* 2007;106(4):687-695.

27. Reade MC, Finfer S. Sedation and delirium in the intensive care unit. *New England Journal of Medicine.* 2014;370(5):444-454.

28. Shehabi Y, Bellomo R, Reade MC, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *American journal of respiratory and critical care medicine.* 2012;186(8):724-731.