Implementation of **N**udges to **P**romote **U**tilization of low **T**idal volume ventilation (INPUT) Study

Sponsor	NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
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Principal Investigator	Meeta Prasad Kerlin MD, MSCE
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Protocol Summary

Title	Implementation of Nudges to Promote Utilization of low Tidal volume ventilation (INPUT) Study
Short Title	INPUT Study
Principal Investigator	Meeta Prasad Kerlin MD, MSCE
Co-Investigators	Rinad Beidas PhD Scott Halpern MD, PhD Barry Fuchs MD Mark Mikkelsen MD, MSCE Dylan Small PhD
Design	Pragmatic, prospective stepped-wedge cluster randomized trial
Objectives	Our primary objective is to compare simple, low-cost, scalable strategies grounded in behavioral economic theory to (a) increase utilization of evidence-based lung-protective ventilation (LPV) to patient who undergo mechanical ventilation (MV), (b) gauge the process-oriented and clinical benefits of targeted vs. non-targeted approaches to changing behavior, (c) explore how clinician and environmental contextual factors affect LPV utilization, and (d) determine how patient factors such as type and severity of disease affect both LPV utilization and its associated outcomes.
Interventions	• **Strategy A: Default order set for MV** With the default order set strategy, a physician will see a different order panel to order mechanical ventilation settings than the current usual state. In this intervention order panel, the ventilation mode will be pre-selected to be assist-control, volume-cycled; and the tidal volume with be pre-populated via an automatic calculation of 6 cc/kg of the patient's ideal body weight (as determined by each patient's height and gender, which are entered into the EHR during every hospital admission). The physician will have the option to opt out of any of the pre-specified settings with one click. • **Strategy B: Physician-targeted accountable justification of MV orders** In this strategy, the order panel will remain nearly identical to the current state, with no pre-specified settings. However, if a physician enters an order for a tidal volume that is greater than 6.5 cc/kg ideal body weight, the physician will be required to enter a reason for choosing a setting inconsistent with LPV into a free text box. This box will instruct them to provide a reason for deviation from LPV settings and would inform them that their response will be maintained in the

	medical record. The physician will not be able to proceed with entering the MV order until after a response is entered. • **Strategy C: RT- targeted accountable justification of initial MV settings** In this strategy, if an RT enters a set tidal volume value greater than 6.5 cc/kg into the flowsheet, he/she will be receive a pop-up window that requests that the RT enter an explicit rationale into a free-text box for deviating from LPV settings, similar to the physician-targeted accountable justification strategy.
Study Duration	27-month trial period, with a minimum 6-month follow-up without intervention monitoring
Study Sites	12 ICUs within 5 hospitals of the University of Pennsylvania Health System (UPHS)
Sample Size	Estimated 9,900 episodes of MV and 100 clinicians
Patient Eligibility	For the purpose of the trial, the analytic sample will be limited to the following: -Aged 18 and over; AND -Undergoing mechanical ventilation Patients eligible according to the criteria above will be EXCLUDED if: -The episode of MV lasts less than 12 hours, because we believe that the evidence-based practice may not apply to these patients nor alter their outcomes. -The patient is on minimal settings for the entirety of MV, defined as a spontaneous mode (e.g., pressure support ventilation) with pressure support <10 cmH2O, AND PEEP <8 cmH20, AND FiO2 <50%, because the clinical significance of spontaneous tidal volumes is unknown and low tidal volumes may not be beneficial or desirable. -Goals of care are documented as comfort measures only (as identified through their "code status" field in the EHR) during the first 72 hours during episode of MV, because mechanical ventilation is managed differently during care focused exclusively on comfort and low tidal volume ventilation may not be appropriate, nor would it likely influence clinical outcomes. -There is no height documented in the EHR at the time of initiation of MV, because we will be unable to estimate ideal body weight, a necessary parameter to calculate the primary outcome, and because they will not receive the interventions. -The height documented is less than 4 feet, because the formula for ideal body weight is not valid below this height.

Outcomes	**Primary outcome variable: Fidelity to low tidal volume ventilation**, defined as percentage of time in the first 72 hours of mechanical ventilation that a patient is exposed to tidal volume >6.5 cc/kg ideal body weight **Major secondary outcome variables:** • MV metrics: Durations of exposure to tidal volume >8 cc/kg and >10 cc/kg ideal body weight; initial tidal volume administered; duration of time exposed to plateau pressure (Pplat)>30 cmH20 • Clinical outcomes: in-hospital mortality, hospital discharge disposition, duration of MV, ICU and hospital length-of-stay • Potential adverse effects of LPV: total cumulative doses of sedative medications during and after mechanical ventilation, total number of days with acute brain dysfunction during and after mechanical ventilation
Analysis of Primary Outcome	• The primary analysis will be performed at the level of the episode of mechanical ventilation. It will follow a modified intention-to-treat approach, such that all patients meeting criteria and exposed to or eligible to be exposed to one of the order panel interventions (which will fire for a new mechanical ventilation order during the period of ICU admission) will be randomized and evaluated in the analysis • Primary analyses will utilize a mixed effects regression models with random effects for ICUs and fixed effects for time to account for the stepped-wedge cluster randomized design, and risk adjustment for several ICU and patient factors to account for potential imbalance due to the design.
Study Oversight	• Trial oversight will be conducted by the University of Pennsylvania (Penn) Institutional Review Board (IRB00000039). • A Data and Safety Monitoring Board (DSMB) will be convened to review the trial protocol and any safety concerns that may arise. • An expert critical care clinician (attending physician, fellow physician, or advanced practice provider) who has been trained by PI Kerlin, in conjunction with project manager Tran, will be directly responsible for identifying and reporting all serious adverse events to the DSMB and the IRB. • PI Kerlin will also report protocol deviations/violations and unanticipated events to the Penn IRB and DSMB. • Unanticipated adverse events that occur at any participating hospitals will be reported by ICU leadership to Co-I Fuchs.

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1. Background and Rationale

1.1 Background and rationale for the INPUT study

Of the million Americans who undergo invasive mechanical ventilation (MV) annually within intensive care units (ICUs),[1-3] 30-35% die in the hospital,[1,4] and survivors commonly have long-term cognitive, emotional and physical impairments.[5,6] Although potentially life-saving, MV can also injure the lungs.[7] Strategies of "lung-protective ventilation" (LPV) aim to minimize harm by delivering low tidal volumes (the amount of air per breath delivered by the ventilator) and limiting the artificial pressures in the lungs. LPV was first proven effective in patients with acute respiratory distress syndrome (ARDS), a severe form of respiratory failure associated with pneumonia, sepsis, and other common illnesses.[8] A multicenter randomized trial published in 2000 demonstrated an absolute mortality reduction of 10%, shortened duration of MV, and reduced organ failure rates.[9] These findings have since been replicated and incorporated into international guidelines.[10] However, over fifteen years later, more than one-third of ARDS patients overall, and up to 81% in some ICUs, do not receive LPV.[11,12]

Multiple studies across diverse ICUs have consistently identified two key barriers to LPV utilization: limited knowledge about LPV,[13-17] and tendencies to prescribe LPV only when ARDS is definitively diagnosed,[14,15] in part due to theoretical concerns about potential harms of LPV.[15] However, definitive diagnosis of ARDS is challenging.[18,19] And recent evidence suggests that (1) concern for harm among patients without ARDS is likely unwarranted,[20,21] and (2) LPV may in fact reduce lung injury and mortality even among patients without ARDS.[22]

2. Objectives

2.1 Primary objective

The study's overall objective is to compare simple, low-cost, scalable strategies grounded in behavioral economic theory to (a) increase utilization of evidence-based LPV for MV patients, (b) gauge the process-oriented and clinical benefits of targeted vs. non-targeted approaches to changing behavior, (c) explore how clinician and environmental contextual factors affect LPV utilization, and (d) determine how patient factors such as type and severity of disease affect both LPV utilization and its associated outcomes.

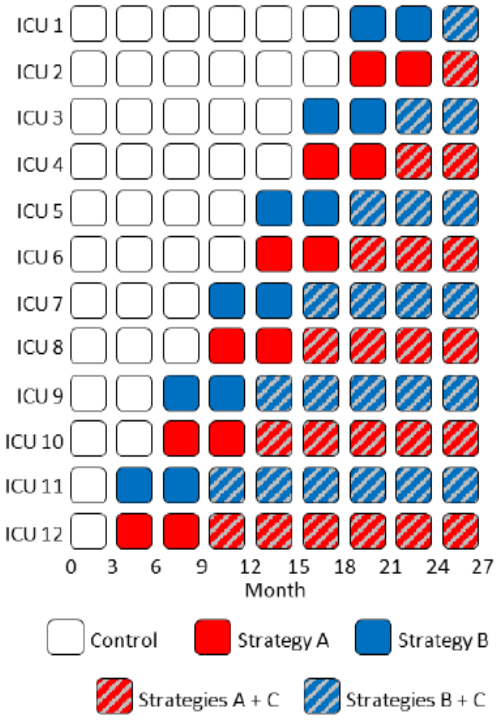
3. Study Design

3.1 Overview

We will perform a stepped-wedge, cluster randomized trial of three EHR-based implementation strategies designed to increase utilization of LPV among MV patients.

During the trial, study ICUs, which at baseline use an EHR-based algorithm to identify patients with ARDS and prompt physicians and respiratory therapists (RTs) to employ LPV, will sequentially add two of three EHR-based implementation strategies to further promote LPV utilization among all MV patients. ICUs will be randomly assigned to first receive one of two physician-directed strategies: either a **default order set (Strategy A)** or **physician-targeted accountable justification strategy (Strategy B)**. ICUs will be randomly assigned to one of six wedges, thereby determining the date on which they adopt their assigned EHR-based strategy (**Figure 3**). The first wedge will begin in the fourth month of the trial phase, so that all hospitals will contribute a minimum of 3 months of data prior to having adopted the

implementation strategy. Six months after adoption, all ICUs will add on an **RT-targeted accountable justification strategy (Strategy C)**. By the end of the 27-month study period, all hospitals will have been utilizing two strategies in combination for at least 3 months. This design enables comparisons of outcomes before and after implementation *within* ICUs, as well as at a given point in time *among* ICUs which will have been randomly assigned to different strategies.[23]



For the objectives of this study, the stepped-wedge cluster randomized design is preferred to designs that randomize individual patients and to parallel or cross-over cluster designs. Patient level randomization is problematic because the intervention entails a systems level modification of clinician behavior, rather than a test of a simple drug or procedure. Individual patient randomization would require that clinicians adhere to three very different approaches, reducing adherence and likely resulting in contamination across arms. Randomizing patients within entire intensive care units to receive the intervention decreases the risks.

3.2 Duration

The study will have a control period, an intervention period, and an observational period. All ICUs will contribute a minimum of 3 months of baseline data prior to intervention and utilize two strategies in combination for a minimum of 3 months. ICUs will be assigned to intervention phase based on the randomization strategy described in detail below. After the intervention period, all study ICUs will contribute at least 6 months of post-intervention data. The total study intervention period will be 27 months and entire study duration will be a minimum of 33 months.

3.3 Study Setting

We will test the intervention during the course of providing usual care among a large and diverse population of patients admitted to 12 ICUs across 5 hospitals within UPHS.

3.4 Eligibility Criteria

The implementation strategies will be rolled out as a **new standard of care for all mechanically ventilated patients admitted to 12 intensive care units**. For the purpose of the trial, patients will be considered initially eligible if they are:
-Aged 18 and over; **AND**
-Undergoing mechanical ventilation

Any patients meeting the eligibility criteria above will be **excluded** from the analysis for the following reasons:
-The episode of MV lasts less than 12 hours, because we believe that the evidence supporting low tidal volume ventilation does not apply to patients who undergo very short periods of MV, nor does it alter their outcomes.

-The patient is on minimal settings for the entirety of the first 72 hours of MV, defined as a spontaneous mode (e.g., pressure support ventilation) with pressure support <10 cmH2O, AND PEEP <8 cmH20, AND FiO2 <50%, because the clinical significance of spontaneous tidal volumes is unknown and low tidal volumes may not be beneficial or desirable.
-Goals of care are documented as comfort measures only during the first 72 hours during the episode of MV, because mechanical ventilation is managed differently during care focused exclusively on comfort and low tidal volume ventilation may not be appropriate, nor would it be expected to influence clinical outcomes.
-There is no height documented in the EHR at the time of initiation of MV, because we will be unable to estimate ideal body weight, a necessary parameter to calculate the primary outcome, and because they will not receive the interventions.
-The height documented is less than 4 feet, because the formula for ideal body weight is not valid below this height.

Clinicians will be eligible for inclusion in semi-structured interviews if they participate in any shift to provide bedside care and interact with one of the three interventions during intervention phase of any study ICU.

3.5 Randomization
All ICUs will receive one of two physician-directed interventions, followed by the RT-directed intervention, as described above. The study design includes randomization at the ICU level.

12 ICUs across five UPHS hospitals will be randomized into six 2-ICU clusters by computerized random-number generation using R random number generator function. To form clusters with balanced patient volume and primary outcome baseline value, ICUs will be matched in pairs based on: 1) ICU patient volume (ICUs will be categorized as large or small based on whether their annual patient volume is above or below the median) and 2) the baseline value of the primary outcome (ICUs will be categorized as high or low rates of adherence to LPV based on whether their median rate is above or below the median). The six ICU clusters will then be randomly assigned to receive either Strategy A or B and then randomly assigned to represent wedges 1 through 6, with each wedge transitioning to the intervention phase in sequential fashion.

3.6 Blinding to study group assignment
The study PI and data analyst will remain blinded to all study group assignments throughout the trial and during the analyses. The data manager and project manager will be unblinded to study group assignments, in order to facilitate data processing and adverse event monitoring and communication with the Data Safety and Monitoring Board. An expert critical care clinician (attending physician, fellow physician, or advanced practice provider) other than the PI will be un-blinded to study group assignment only as needed in order to perform detailed reviews of any occurrences of potential serious adverse events (as further detailed below). They will communicate any relevant adverse events to the project manager, who will in turn communicate directly with the DSMB. At the end of the trial, the data manager will assign variables to indicate the study group assignment and time that will allow the data analyst to maintain blinding.

Some of the co-investigators are attending physicians in some of the study ICUs and will potentially be on-service during the trial period. As attending physicians, they typically have no interaction with placing

or reviewing orders in the EHR; therefore, it is unlikely that they will unwittingly be unblinded through their clinical responsibilities.

3.7 Interventions

ICUs, which have individual practices for identifying eligible patients and administering LPV, will sequentially implement two of three EHR-based strategies to further promote LPV utilization among all MV patients. Strategies will be rolled out via a stepped-wedge design. Study ICUs will be randomly assigned to first receive either a **default order set (Strategy A)** or **physician-targeted accountable justification strategy (Strategy B)**. Six months after Strategies A and B are implemented, ICUs will add on an **RT-targeted accountable justification strategy (Strategy C)**.

Strategy A: Default order set for MV

With the default order set strategy, a physician will see a different order panel to order mechanical ventilation settings than the current usual state. In this intervention order panel, the ventilation mode will be pre-selected to be assist-control, volume-cycled; and the tidal volume with be pre-populated via an automatic calculation of 6 cc/kg of the patient's ideal body weight (as determined by each patient's height and sex, which are entered into the EHR during every hospital admission). The physician will have the option to opt out of any of the pre-specified settings with one click.

Strategy B: Physician-targeted accountable justification of MV orders

In this strategy, the order panel will remain nearly identical to the current state, with no pre-specified settings. However, if a physician enters an order for a set tidal volume that is greater than 6.5 cc/kg ideal body weight, the physician will be required to enter a reason for choosing a setting inconsistent with LPV into a free text box. This box would instruct them to provide a reason for deviation from LPV settings and will inform them that their response will be maintained in the medical record. The physician will not be able to proceed with entering the MV order until after a response is entered.

Strategy C: RT- targeted accountable justification of initial MV settings

In this strategy, if an RT enters a set tidal volume value greater than 6.5 cc/kg into the flowsheet, he/she will receive a prompt to enter an explicit reason for deviating from LPV settings, similar to the physician-targeted accountable justification strategy.

After completion of the trial intervention period (27 months in total) we will continue to collect patient data from study ICUs regarding adherence to lung-protective ventilation, use of the implementation strategies, and outcomes, in order to measure sustainment for at least 6 months after the intervention period ends. During this period, the study team will have no interactions with the clinical teams or leadership of the ICU, and no research-related changes will be made to the EHR.

3.8 Data Collection

All research patient data for this pragmatic clinical trial will be captured electronically via the UPHS EHR. Thus, consistent with the goals of a pragmatic trial, there are no research personnel located onsite at each study hospital. Instead, outcomes data will be restricted to data elements that are routinely collected in the course of providing routine clinical care and extracted from the UPHS EHR.

This study also seeks to understand how the implementation strategies function in the context of different clinician and environmental factors, including additional barriers and facilitators of LPV

utilization. During the two months after the implementation strategy rolls out in each ICU, we will perform semi-structured interviews of all physicians and RTs who staff study ICUs. All interviews will be completed by a single research coordinator, who will be trained in the conduct of semi-structured interviews. The interviews follow a guide and begin with neutral, open-ended questions, followed by questions that arise from clinicians' responses, with the interviewer pursuing themes, probing for further details, and seeking clarification and elaboration when appropriate. All interviews will be audio-recorded with the participants' consent and professionally transcribed. No identifiable information will intentionally be collected but may be recorded during the interview. Any identifiable information in interviews will be removed in transcription.

3.9 Outcomes

3.9.1 Primary outcome variable(s)

The primary outcome variables will be (1) **fidelity** to LPV, measured by the percentage of time in the first 72 hours of mechanical ventilation that a patient is exposed to tidal volume >6.5 cc/kg ideal body weight and (2) **sustainability**, measured as the percentage of time in the first 72 hours of mechanical ventilation that a patient is exposed to tidal volume >6.5 cc/kg ideal body weight among MV patients each month during the sustainment period, at least 6 months after the intervention period ends.

3.9.2 Secondary outcome variable(s)

We will include additional measures of LPV as secondary implementation outcome measures:

- Durations of exposure to tidal volume >8 cc/kg ideal body weight
- Duration of exposure to tidal volume >10 cc/kg ideal body weight
- Initial tidal volume administered
- Initial plateau pressure (Pplat)

We will also evaluate the following clinical outcomes:

- In-hospital mortality
- Hospital discharge disposition
- Duration of MV
- ICU length-of-stay
- Hospital length of stay

We will evaluate the potential adverse effect of excessive sedation with LPV using the following additional secondary outcome measures:

- Early deep sedation, defined as the proportion of time during the first 72 hours of mechanical ventilation that patients were alive, in the ICU, and with a RASS -3 to -5
- Average sedation intensity within the first 72 hours, defined as the average RASS value, weighted by duration of time at that value
- Deep sedation for the entirety of the first 72 hours of mechanical ventilation (binary)

4. Trial Implementation

4.1 Participant recruitment and enrollment

All patients admitted to the study ICUs who meet eligibility criteria specified above during the 27-month interventional phase will be enrolled in the study and included in the interventions. Subsequently, all patients meeting the same criteria during the 6-month observational period will be included in the second, observational phase of the study. All patients will be identified through the electronic health record.

We will identify clinicians eligible for participating in interviews during the intervention roll-out periods by building EHR based reports that will generate lists of clinicians who interact with study interventions within all study ICUs. We will recruit clinician participants by sending an email describing the study, explaining that their involvement will require a 15- to 30-minute interview either by telephone or on site at the ICU. Conservatively, we anticipate that we will be able to complete 6 - 8 clinician interviews per wedge over the study intervention period. We will purposively sample and recruit clinician participants to ensure representation of the diverse professional backgrounds and views of the entire population of clinicians in those ICUs.

4.2 Waiver of Informed Consent

The INPUT study will be conducted under a waiver of the requirement for informed consent based on the following criteria set forth by the Federal Policy for the Protection of Human Subjects (the "Common Rule"):

1. The research involves no more than minimal risk to subjects.
2. The waiver will not adversely affect the rights and welfare of the subjects.
3. To the extent possible, the subjects will be provided with pertinent information after participating in the trial.
4. The research cannot be practicably conducted without a waiver of the requirement for informed consent.

<u>The research involves no more than minimal risk to subjects</u>.

The risk to subjects of participating in the trial is no more than minimal because the intervention consists of EHR-based nudges to promote LPV, which is within the standard of care for MV patients. The only manipulation is that LPV ordering may be made simpler and more routine, rather than left to the complete discretion of physicians.

The risk to subjects of participating in the post-trial observational period is also no more than minimal because they will not be subject to any interventions during this phase of the study, and the data that will be collected for analysis will include only data routinely collected for clinical care. The primary risk will be breach of confidentiality of protected health information, and strong safeguards will be put in place to mitigate this risk, as described throughout this protocol.

The risk to subjects participating in clinician interviews is also no more than minimal. The primary risk is the risk of breach of confidentiality about any comments made regarding the quality of care provided in the ICU or the clinicians ICU environment; however, there are strong data safeguards in place to prevent confidentiality breaches.

The waiver will not adversely affect the rights and welfare of the subjects.
The waiver will not adversely affect the rights and welfare of patients because LPV is within the standard of care for MV patients. We do, however, recognize the possibility that some may perceive the intervention to limit the autonomy of physicians to order MV settings; however, this is not the case. Although the EHR-based nudges are designed to prompt clinicians to consider LPV setting for their patients, clinicians still retain decisional autonomy and can use their clinical judgment to order MV settings as they see fit for patient care.

The waiver will not adversely affect the rights and welfare of the clinicians because they will be offered the options to decline participation in the interview, to terminate the interview at any time, and to withdraw their recording or transcript at any time.

To the extent possible, the subjects will be provided with pertinent information after participating in the trial.
Patients enrolled in the study will not be informed of the study as randomization occurs at the ICU unit level, not patient. We have strongly considered viable approaches to satisfy this criterion that is both practical and protective of patients' rights. Under usual care, patients would not be consulted in real-time by their critical care physicians regarding chosen MV settings, or informing them on chosen decision after the fact. Thus informing them of this technical information afterward could cause unnecessary patient or family member distress. This same approach was used in PI Kerlin's pragmatic trial of nighttime intensivist staffing in ICUs, which yielded a study published in the New England Journal of Medicine in 2013.

Materials will be developed for dissemination to ICU staff through the preferred communication channels at each study hospital (e.g. electronic presentations, email, etc.) highlighting the new EHR processes. The stepped-wedge design provides ample time for the investigative team to prepare each hospital individually for implementation of the intervention(s) within their ICU(s). Clinicians will be informed of all study information and subject rights prior to proceeding with the semi-structured interview.

The research cannot be practicably conducted without a waiver of the requirement for informed consent.
This study seeks to evaluate the effectiveness of the intervention for the overall population of MV patients rather than to evaluate efficacy of the interventions for a selected, non-representative subset. The study design calls for randomization by ICU, not by individual patients. It is not technically possible to apply the interventions to some patients in an ICU but not others because they are order sets that must represent the single available order set for MV order entry within the EHR for a given ICU. Furthermore, because many patients will be mechanically ventilated at the time of ICU admission, orders for MV settings will have to be entered within 15 minutes of arrival, per health system policy. Thus, even if there was a role for informed consent, it could not practicably be obtained in this time period. These are the most prominent reasons that it is impracticable to answer the research question without a waiver of informed consent. A secondary, but also relevant consideration is the impracticality of hiring and retaining sufficient staff to obtain individual informed consent at all hours of the day over 27 months at 12 different ICUs. This is wholly inconsistent with the goals of pragmatic clinical trials.

4.3 Waiver of HIPAA Authorization

The INPUT study will be conducted with a waiver of HIPAA authorization in accordance with the provisions for using protected health information (PHI) set forth in 45 CFR 46, § 164.512 (i) as follows:

1. The researchers require access to protected health information (PHI) in order to conduct the research.
2. The research cannot be practicably conducted without the waiver.
3. The use or disclosure of PHI poses no more than minimal risk to participants.

The researchers require access to protected health information (PHI) in order to conduct the research.
The investigative team will analyze a data set derived directly from administrative and electronic health data collected in the course of providing routine clinical care. The research could not be practically done without access to PHI as multiple datasets and data from multiple time points need to be linked in order to identify eligible patients from study ICUs and evaluate the variety of outcomes to answer our study questions. The study is using the minimum necessary elements of PHI to enroll eligible ICU patients and accomplish research objectives.

The research cannot be practicably conducted without the waiver.
This large, pragmatic clinical trial will be conducted within the usual clinical care setting and utilizes existing EHRs rather than research personnel. The research is not practicable without a waiver of HIPAA authorization. The will be conducted within the usual clinical care setting for seriously ill hospitalized patients requiring MV, and their clinicians, and will test an intervention implemented by existing electronic medical records, rather than research personnel. Given these constraints, the research team did not identify a suitable mechanism for notifying the clinicians without introducing important selection biases and contamination as discussed above, or patients and families that is both practical and protective of additional PHI. However, viable approaches to provide subjects with a written statement of research were strongly considered, but there is no clear way for this to be carried out without compromising patient confidentiality or by overburdening clinical staff. In order for investigators to coordinate patient notification, additional PHI about patients and families would be required. Therefore it is more prudent to forego such notification and maintain anonymity of patient data.

The use or disclosure of PHI poses no more than minimal risk to the privacy of individuals because a) processes will be in place to protect PHI from improper use or disclosure; b) PHI will be destroyed at the earliest possible time; and c) there will be no improper use or disclosure of PHI.

5. Data Management

5.1 Data Confidentiality

The Penn Data Manager will collaborate with his/her informatics analyst counterparts within the Penn Data Analytics Center (DAC) and Penn Information Services (IS) to formalize secure data protocols for regular transfer of EHR data from DAC and IS to the Palliative and Advanced Illness Research (PAIR) Center's secure fire-walled server, with restricted access by the Penn Data Manager and appropriate analytic staff. Data transfer is transmitted via Penn's Secure Share, whereby files are encrypted when they are uploaded, downloaded, and while being stored. Qualitative data from clinician interviews will be transcribed and maintained in an NVivo database on the secure server with removal of all identifiers and deletion of original audio files.

We will implement multiple, redundant protective measures to guarantee the privacy and security of the patient data. All data for this project will be stored on the secure and firewalled servers of UPHS and PMACS in data files that will be protected by multiple password layers. These data servers are

maintained in guarded facilities behind several locked doors, with very limited physical access rights. They are also cyber-protected by extensive firewalls and multiple layers of communication encryption. Electronic access rights are carefully controlled by Penn system managers. This multi-layer system of data security, identical to the system protecting the UPHS' medical records, greatly minimizes privacy risks.

5.2 Subject Confidentiality

Only authorized project personnel will have access to the data. All study data will be stored behind firewalls on computer servers; none will be stored on stand-alone PCs or laptops. Clinical trial data will be transferred using secure data transfer protocols from the Penn Medicine Data Analytics Center (DAC) and Penn Information Services (IS) to the Palliative and Advanced Illness Research (PAIR) Center on a monthly basis.

All recorded interviews will be professionally transcribed and personal identifiers removed before uploading to an NVivo 11 database. All study databases will be hosted on secure servers, managed by the PAIR Center Data Manager, and restricted to only those individuals who are authorized to work on the trial. Additional measures to prevent unauthorized external access to the database environment will be employed using network firewall technologies.

5.3 Subject Privacy

All patient data for this study will be obtained from the EPIC electronic medical record. It is information that is routinely documented by clinical nurses during patient care. During routine care such as patient rounds, clinicians and the research team will maintain the same HIPAA standards that are currently used in daily clinical practice.

Semi-structured interviews were chosen to protect subject privacy while collecting clinician data. In addition, all semi structured interviews will be conducted in a private location or by telephone and completed by a single research coordinator, who will be trained by Dr. Kerlin in the conduct of semi-structured interviews. All clinicians who staff the ICUs will be recruited through existing staffing lists and asked to complete an interview and retain the autonomy to decline. They will also be informed that their responses will not be shared with any identifying information with their supervisors and that any data shared with supervisors or ICU leaders will only be in aggregate form so as to protect their privacy.

6. Human Subjects Protection

6.1 Risk / Benefit Assessment

The potential risks to human subjects include: 1) risks of breach of confidentiality of personal health information; The Common Rule is fairly clear that the incremental risk standard is the appropriate one (1), noting that in evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). Accordingly, the first risk listed above (breach of confidentiality) is germane to considerations of the risks of this research. (2) risks that the interventions could have untoward impacts on patients or their family members. Potential untoward impacts include the potential risk of adverse consequences of LPV, which may increase in use due to the intervention. Because LPV is used heterogeneously for patients with and without ARDS in standard practice, risks of LPV could be considered within the "therapies subjects would receive even if not participating in the

research" and hence ought not be considered risks of the research per se. Evidence suggests that LPV benefits mechanically ventilated patients, and although there are theoretical concerns regarding adverse consequences such as increased sedative needs for ventilator discomfort, such concerns have never been substantiated and available evidence suggests that they are not founded. Furthermore, as experts advocate for broader application of LPV, many patients could, and arguably should, receive LPV in the absence of a trial. Thus, the interventions studied are within the current range of standard of care.

6.2 Protective Measures

The first safeguard for protection of patients includes an experienced and well-trained study team. The study's principal investigator (PI), **Dr. Meeta Prasad Kerlin**, is Assistant Professor of Medicine at the University of Pennsylvania (UPenn). She has considerable expertise in research focused on ICU organization and the care of mechanically ventilated patients. She co-led (with Co-Investigator Halpern) an ICU-based randomized clinical trial published in the *New England Journal of Medicine,* and was a co-investigator on a CDC-funded multicenter implementation of an opt-out strategy to improve evidence uptake for sedative management and MV weaning. She is also funded by the NIH for work focused on the identification of barriers and facilitators of prone-positioning, another proven effective intervention for ARDS (R03 HL144890). Co-Investigator **Dr. Scott Halpern** is Professor of Medicine, Epidemiology, and Medical Ethics & Health Policy. He has collaborated with Dr. Kerlin on the aforementioned RCT and numerous other ICU-based studies. He is Director of the Palliative and Advanced Illness Research (PAIR) Center and a member of the Steering Committee of Penn's Center for Health Incentives and Behavioral Economics. He has extensive expertise in developing and testing behavioral economics interventions to change healthcare delivery. He is currently leading several multicenter randomized trials using behavioral economic and EHR-based strategies to improve care delivery. Several key members of the Palliative and Advanced Illness Research Center will contribute to this project: Teresa Tran, Jasmine Silvestri, Stefania Scott, and Wei Wang, who all have experience working with pragmatic clinical trials among seriously ill patients.

All patient research data for this pragmatic clinical trial will be obtained from the EPIC electronic medical record, through chart review. The EPIC databases will be hosted on secure Penn Medicine Academic Computing Server and will be restricted to only those individuals who are authorized to work on the trial. Authorized users are knowledgeable and experienced in secure data management and confidentiality and will remain up to date on their Human Subjects Research Protection training. Dr. Kerlin will provide oversight for all authorized users. Individual user accounts with passwords will be used to restrict access to databases. Specific privilege assignments within databases will also be employed to limit the types of functions that authorized users can perform to those functions that are appropriate for their roles in the trial. Additional measures to prevent unauthorized external access to the database environment will be employed using network firewall technologies. All analytic databases will be de-identified.

All study investigators have completed online training programs in the Responsible Conduct of Research and Health Insurance Portability and Accountability Act (HIPAA) certification in accordance with Penn regulations. All members of the study team will maintain active certifications throughout the study. Online training (the Collaborative Institutional Training Initiative [CITI]) is divided into a number of rubrics including: data acquisition and ownership; materials and their ownership; intellectual property; authorship; peer review; collaborative science; human subjects; environmental safety; research misconduct; conflict of interest; and research administration. Each rubric includes institutional and

federal policies, lectures, and interactive quizzes. In aggregate, these materials provide systematic training in the fundamental issues underlying the responsible conduct of research.

All patient research data for this pragmatic clinical trial will be obtained from the EPIC electronic medical record, through chart review. The EPIC databases will be hosted on secure Penn Medicine Academic Computing Server and will be restricted to only those individuals who are authorized to work on the trial. Authorized users are knowledgeable and experienced in secure data management and confidentiality and will remain up to date on their Human Subjects Research Protection training. Dr. Kerlin will provide oversight for all authorized users. Individual user accounts with passwords will be used to restrict access to databases. Specific privilege assignments within databases will also be employed to limit the types of functions that authorized users can perform to those functions that are appropriate for their roles in the trial. Additional measures to prevent unauthorized external access to the database environment will be employed using network firewall technologies. All analytic databases will be de-identified.

7. Sample Size and Analysis Plan

7.1 Sample Size

The study will involve three groups of human subjects.

The first group includes mechanically ventilated patients admitted to study ICUs during a pragmatic trial of interventions that will be applied at the level of the ICU. Patients will not be approached directly for inclusion in this study. The interventions will be embedded within the electronic health record that is in use at each hospital. The sample size will be determined by the number of eligible patients that are admitted to study ICUs during the study period, which we estimate will be 27 months during the trial monitoring period. An estimated 6000 patients undergo MV annually within 13 ICUs of the 6 hospitals of UPHS. By extrapolating these data to a 27-month enrollment period, excluding one ICU for strategy development and pilot- testing, and excluding a fraction of patients who will meet exclusion criteria specified above, at the start of the study, we estimated that approximately 8,000 MV patients will be eligible for inclusion in the trial across the remaining 12 ICUs during the study's intervention period. At the time of the first interim analysis, after 9 months of enrollment and with more refined and precise data extraction and patient exclusion, we revised our projected estimates to 6900 patients who meet eligibility criteria during the intervention period.

The second group includes clinicians who are practicing within study ICUs during the intervention period. Clinicians, including physicians, advanced practice providers, respiratory therapists, and ICU leaders, will be approached for participation in semi structured interviews to elicit their perceptions of the implementation strategies. We anticipate enrolling 5 to 10 clinicians per ICU, with approximately 100 total.

The third group includes mechanically ventilated patients admitted to study ICUs in the 6 months after intervention phase has been completed. During this observational phase, there will be no experimental interventions. Study ICUs will be free to design and implement processes of care entirely at their discretion. Patients will be included in the analysis if they meet eligibility criteria, which will be identical to those of the first interventional phase of the study. By extrapolating estimated enrollment data to a -6 month enrollment period, we estimate this will include approximately 1,600 MV patients.

7.2 Statistical Analysis

Full details are provided in a separate Statistical Analysis Plan document.

7.2.1. Primary Analytic Approaches

The primary analytic approach will use a **modified intention-to-treat (MITT)** approach. We choose this approach because we have observed in preliminary studies in the study ICUs that some patients will start MV and receive MV orders prior to ICU admission, and because of the constraints of the EHR to deploy the strategies, these episodes will not be eligible for exposure to the study interventions, which only "fires" with new MV orders. Because ICUs differ in their percentages of patients who will and will not be exposed to the strategies, and these patient groups may be systematically different, the primary analysis will include patients who have a new MV order after the time of ICU admission.

We will repeat the primary analyses using two secondary analytic samples. The first will include the true ITT population; that is, the entire population of episodes of MV in any study ICU (after exclusions detailed above), regardless of whether or not there was exposure to an implementation strategy during the intervention period. This analysis will provide insight into how ICU-targeted strategies may influence the strategies' effectiveness. We hypothesize that the effect of the strategies to improve administration of low tidal volumes will be attenuated in the true ITT population, compared to the modified ITT population. The second will include a per-protocol population; that is, only those episodes in which clinicians were actually exposed to the study interventions. We hypothesize that the effect of the strategies to improve administration of low tidal volumes will be enhanced in the per protocol population, but studying this population alone will not yield accurate information of the effectiveness in real-life settings where circumventing the nudges may be possible.

The unit of analysis for the primary study outcome and all implementation outcomes will be the episode of mechanical ventilation. Patients may have multiple episodes of MV if the patient is ventilated multiple times. We will include only the first eligible episode during a hospital admission for the primary analysis. We will calculate the proportion of patients who receive multiple episodes or multiple admissions. We expect the proportion will be very small, based on prior data from study ICUs. In a sensitivity analysis, we will include all episodes of mechanical ventilation, including subsequent episodes for the same patient. There will be a small percentage of patients for whom the ICU undergoes a transition from control to an intervention, and a small percentage who are transferred from one ICU to another that has a different assignment. For primary analyses, the exposure group will be assigned according to the status of the admitting ICU (e.g., control or intervention assignment) at the time of the initiation of MV and ICU admission.

All of the MITT, ITT, and per protocol analyses will be conducted with adjustment for the following pre-specified, patient-level covariates that exist prior to randomization: age, gender, ICU admission source, a modified Laboratory-based Acute Physiology Score, version 2 (LAPS2) severity of illness, duration of hospitalization prior to ICU admission, location of initiation of MV (i.e., within study ICU or prior to ICU admission), and code status (i.e., the presence or absence of do-not-resuscitate or other treatment-limiting orders).

During the trial, one of the hospitals plans to open a new hospital tower, which will result in physical relocation and possible expansion of two study ICUs, as well as other organizational changes that may impact study variables (such as changes to nighttime coverage by critical care specialists). To account for

this occurrence, we will include a fixed effect for whether or not patients at this hospital were enrolled before or after the date that the hospital tower opens.

In addition, in recognition of the fact that this trial will commence during the COVID-19 pandemic, and that ICUs may be altered in response to any surges of critically ill patients with COVID-19, we will *a priori* plan to include a fixed effect for any period of time of alterations in policies affecting mechanically ventilated patients due to COVID-19. Based on prior pandemic policies, this will include any periods of time in a hospital when (1) new, temporary ICUs are opened; (2) any ICUs are closed, and (3) restrictions placed on elective procedure scheduling, as these changes could influence the MV patient populations and workflow in unpredictable ways.

For the primary outcome we will use mixed effects linear regression models with random effects for ICUs and fixed effects for time to account for the stepped-wedge cluster randomized design. The following comparisons are the primary comparisons of interest: control vs. strategy A, control vs. strategy B, strategy A vs. strategy B, strategy A vs. strategy A combined with strategy C, and strategy B vs. strategy B combined with strategy C. In addition, we will conduct secondary analyses to compare control vs. A+C, control (strategy A combined with Strategy C, an accountable justification targeting respiratory therapists), and control vs. B+C. The treatment group of each episode of mechanical ventilation will be assigned according to the intervention status of the admitting ICU (control group, or strategy A, B, A+C or B+C) at the time of initiation of mechanical ventilation.

We will use the Holm method to assess the between-arm contrasts of interest by sequentially testing the significance of each against progressively less restrictive alpha levels, preserving the family-wise Type I error rate of 5%. We will perform a sensitivity analysis including fixed effects for ICUs to account for the possibility of ICU-level confounding. We will build similar linear regression models for all continuous secondary outcomes and logistic mixed effects regression models for binary outcomes.

7.2.3. Analyses of patient level factors

Patient-level effect modification will be explored by repeating the analyses of the primary outcomes stratified by the two candidate effect modifiers described in detail above: presence or absence of ARDS and degree of hypoxia (as measured by the P:F ratio, calculated as the PaO_2 divided by the fraction of inspired oxygen (FiO_2)). If differences appear in stratified analyses, we will formally evaluate for effect modification by testing the significance of coefficients for statistical interaction terms between the potential effect modifier and the study groups on the primary outcome of LPV utilization, and on a subset of effectiveness outcomes: in-hospital mortality, hospital length of stay, and sedation measures. Finally, we will conduct subgroup analyses by race/ethnicity and sex/gender to determine the presence of effect modification on outcome.

7.2.4. Analysis of clinician and environmental contextual factors

To explore how the strategies interact with clinician and environmental contextual elements, we will conduct voluntary, semi-structured interviews with ICU clinicians (ordering clinicians and RTs) during the first three months after strategy implementation in each study ICU. A research coordinator trained in qualitative interviewing will use a semi-structured script guided by several constructs of the Consolidated Framework for Implementation Research (CFIR) domains of characteristics of the individual, inner setting, and process to elicit perceptions of the implementation strategies and identify factors that may influence the success of the strategies to improve adherence to LPV. For example, in order to understand how individual clinician characteristics interact with each strategy, we will ask them

about their knowledge of LPV and prior experience and comfort with managing MV patients. To understand the role of the inner setting factors, we will inquire about how ICU leadership influences LPV utilization, for example, as well as communication and teamwork between different professional groups involved in MV management.

All interviews will be audio-recorded with the participants' consent and professionally transcribed. Two research staff members will code transcripts from interviews. We will use the CFIR framework as a preliminary codebook 35 and add themes and subthemes specific to the data as they arise. We will assess inter-coder reliability by double-coding every fifth transcript. The qualitative analysis will help us to identify the most likely relevant factors associated with implementation of LPV. We will then test these theories using quantitative analyses.

After developing a discrete set of clinician factors from interviews (such as level of experience, assigned to ICU versus rotating responsibilities), we will assign them to clinicians and evaluate whether they modify the effects of the implementation strategies quantitatively using the sample of patients cared for by participating clinicians during the trial. To do so, we will first repeat the primary analysis stratified by clinician factors. If we find evidence of differences in the effect sizes, we will add multiplicative interaction terms for each clinician factor with the implementation strategy in the models to quantify whether interactions are significant. To explore the role of ICU factors, we will similarly perform quantitative analyses stratified by ICU. After developing a discrete set of environmental factors from interviews, we will assign them to ICUs and explore whether any patterns emerge.

7.3. Approach to Missing Data

Based on preliminary analyses of missingness within a retrospective cohort of MV patients admitted to 11 of 12 study ICUs, we propose the following approaches to missing data, based on specific data elements:

-Missing or erroneous value for ideal body weight: Less than 5% of patients in a retrospective patient cohort including 11 of 12 study ICUs have either missing or erroneous data for patient height, which results in a missing or erroneous value of ideal body weight. Because the EHR-based implementation strategies will not function for patients with missing data for height (i.e., there will be no pre-populated value for tidal volume, or threshold to trigger the accountable justification prompts), we will exclude these patients from the primary analysis and will report the percentage of missingness in the results.

-Missing data for ventilator settings: Ventilator flowsheet data are entered at variable intervals, depending on clinical circumstances (e.g., if a patient's settings are changed) and routine practice (e.g., the ICU documentation standards). Therefore, there are no regular intervals during which ventilator flowsheet data will be entered. At any given time point, some or all relevant ventilator data may or may not be entered by a respiratory therapist or nurse. If ventilator data settings are partially missing for a given time (e.g., one setting or parameter is documented but others are not at a certain time), we will use single imputation, carrying forward data from the prior time of documentation for any relevant parameters that are missing. We choose this strategy because we suspect that if a setting or parameter is not documented at a subsequent time, then that setting or parameter is unlikely to have changed (i.e., a change in a setting or parameter would typically prompt documentation).

-Missing or erroneous data for potential confounders, including severity of illness measures: In our previous experience working with data from the retrospective cohort, we anticipate minimal missingness for variables that will be included in severity of illness measure (LAPS2). In the rare event

that we do have missingness for a parameter included in an acute physiology score, we will use single imputation of a normal value for that parameter, as is the common approach in calculation of severity of illness measures. This strategy would bias the results towards the null. We will report percentage of missingness and discuss the risk of bias in the limitations.

7.4. Statistical Power Calculations

We estimated the power of pairwise comparisons of any of the intervention groups (Strategy A or B alone or in combination with C – i.e., four separate intervention groups) with the control group. We initially based our power calculations on the following conservative assumptions: sample size of 8,000 episodes across 12 ICUs; an intracluster correlation within ICUs of 0.1; and a baseline mean value of the primary outcome of 45% with a standard deviation of 45% (based on estimates from a retrospective cohort of patients admitted to ICUs in study hospitals during a 6-month period in 2020, including patients with COVID-19). With these assumptions, we estimated that we will have >95% power to detect an increase of 25% in the mean value of the primary outcome (from 45% to 70%), which would approximate the utilization rates of the study ICU with the highest adherence to tidal volume < 6.0ml/kg ideal body weight. This sample size also has >90% power to detect a difference of 20% and nearly 80% power to detect a difference as low as 15% in any pairwise comparisons. Finally, this sample size has 80% power to detect a reduction in in-hospital mortality from an estimated 25% to 16%.

At the time of the first interim analysis, based on the rate of accrual during the first 9 months of the trial and with application of more precise exclusion criteria, we found that the number of eligible patients admitted to study ICUs was lower than projected. Therefore, we repeated power calculations with smaller estimated samples sizes of 5100 for the MITT (primary) population and 6900 for the ITT population. With these new estimates, and using the same assumptions as above, we estimated that we have at least 97% power to detect an increase of 25% in the mean value of the primary outcome (from 45% to 70%) and greater than 80% power to detect an increase as low as 17% in the mean value of the primary outcome within the MITT population. In addition, the new estimated MITT sample size has approximately 80% power to detect an 11% reduction in hospital mortality from an estimated 25% to 14%.

8. Data and Safety Monitoring

8.1. Adverse Events and Unanticipated Problems

The study team will be responsible for identifying and reporting all serious adverse events, protocol deviations/violations, and unanticipated problems to the IRB, DSMB, and funding agency promptly, as appropriate. In order for the PI to remain blinded, expert critical care clinicians (attending physician, fellow physician, or advanced practice provider) trained by PI Kerlin will lead adverse event monitoring and reporting, with the support of the project manager. We will proactively perform surveillance of three adverse events – life-threatening acidemia, and death or cardiac arrest within 24 hours of trial enrollment. Adverse events possibly or likely related to the intervention will be reported immediately to the Data and Safety Monitoring Board (DSMB, see below) within 7 days of occurrence, if fatal or life-threatening. Unanticipated problems will be reported to DSMB within 14 days of identification.

8.2. Data and Safety Monitoring Board

An important safeguard to protect research participants is the development of a plan for ongoing data and safety monitoring to anticipate, and protect against, any human subjects research concerns that

may arise. We will convene a DSMB comprising noted experts in critical care, palliative care, and biostatistics to guard against the possibility of any unforeseen risks arising during the study. Members of the DSMB will not be involved in the conduct of the trial. Once convened, the DSMB will perform several duties. First, they will review and approve the research protocol and plans for data and safety monitoring prior to the study's implementation. Second, they will evaluate the progress of the trial. This will include assessment of data quality, participant accrual and retention, participant risk versus benefit, and study outcomes. Third, they will make recommendations to ensure that any identified issues are appropriately addressed. The DSMB will meet after 9 months and 18 months (one-third and two-thirds of the way through the trial enrollment. We will charge DSMB members with using their judgment in simultaneously considering many data points in making decisions about trial design modifications and trial continuation or termination. The PI (Dr. Kerlin), the project manager, and the data analyst (Dr. Wang), will participate in all DSMB meetings as non-voting members. The PI, assisted by the project manager, will be responsible for maintaining communication between the DSMB, the IRB, and study sites.

Our DSMB members to monitor the scientific conduct of the study are as follows:

- **Todd Rice**, **MD, MSc** Associate Professor of Medicine in the Division of Allergy, Pulmonary and Critical Care Medicine at Vanderbilt University (DSMB Chair)
- **Daniella Meeker, PhD** Assistant Professor of Preventive Medicine and Director of Clinical Research Informatics at the Keck School of Medicine University of Southern California
- **Kristin Riekert, PhD** Professor of Medicine in the Division of Pulmonary and Critical Care Medicine, Department of Medicine at Johns Hopkins University and Director of the Johns Hopkins Adherence Research Center (JHARC) and the Director of the Cystic Fibrosis Adherence Program
- **Jing Cheng, MD, MS, PhD** Professor of Biostatistics within the University of California San Francisco Division of Oral Epidemiology & Dental Public Health and Division of Epidemiology and Biostatistics

8.3. Interim Analyses

The trial will be monitored routinely for issues of data quality and study conduct (including participant enrollment and technical issues with EHR order sets) via monthly data extraction and analysis by our research team's data manager, Stefania Scott. We will conduct two interim analyses – after approximately 9 months and 18 months (one-third and two-thirds of the trial duration, respectively) – of two study outcomes: (1) fidelity to LPV (primary outcome, as specified above), and (2) in-hospital mortality.

We do not plan to stop the trial early for evidence of effectiveness of the implementation strategies because doing so would reduce our power for secondary analyses and analyses of effect modification. We will propose to stop the trial for early evidence of harm based on in-hospital mortality.

8.4. Institutional Review Board (IRB)

The convened University of Pennsylvania IRB (FWA: 00004028) have approved the INPUT study (#833340) with a waiver of informed consent and waiver of patient notification. Penn IRB will provide regulatory oversight for the trial activities at the study hospitals. All modifications to the protocol will be submitted to both IRBs for approval prior to implementation.

8.5. Clinicaltrials.gov

The INPUT study is registered on clinicaltrials.gov (NCT04663802). Although not required by law for clinical trials not involving drugs or devices, trial registration is required by the International Committee of Medical Journal Editors (ICMJE) as a condition of the publication of research results generated by a clinical trial and by the National Institutes of Health (NIH) for all funded clinical trials. The study profile will be regularly updated on the website and summary results uploaded to make information about the study publicly available and promote transparency.

9. References

1. Wunsch H, Linde-Zwirble WT, Angus DC, Hartman ME, Milbrandt EB, Kahn JM. The epidemiology of mechanical ventilation use in the United States. Crit Care Med 2010;38:1947 53.
2. Kerlin MP, Weissman GE, Wonneberger KA, et al. Validation of Administrative Definitions of Invasive Mechanical Ventilation across 30 Intensive Care Units.Am J Respir Crit Care Med 2016;194:1548-52.
3. Wunsch H, Kramer A, Gershengorn HB. Validation of Intensive Care and Mechanical Ventilation Codes in Medicare Data. Crit Care Med 2017;45:e711-4.
4. Esteban A, Anzueto A, Frutos F, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 2002;287:345-55.
5. Bienvenu OJ, Colantuoni E, Mendez-Tellez PA, et al. Depressive symptoms and impaired physicalfunction after acute lung injury: a 2-year longitudinal study.Am J Respir Crit Care Med 2012;185:517-24.
6. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. N Engl J Med 2013;369:1306-16.
7. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. New Engl J Med 2013;369:2126-36.
8. Villar J, Blanco J, Anon JM, et al. The ALIEN study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. Intensive Care Med 2011;37:1932-41.
9. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. New Engl J Med 2000;342:1301-8.
10. Fan E, Del Sorbo L, Goligher EC, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome.Am J Respir Crit Care Med 2017;195:1253-63.
11. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA 2016;315:788-800.
12. Weiss CH, Baker DW, Weiner S, et al. Low Tidal Volume Ventilation Use in Acute Respiratory Distress Syndrome. Crit Care Med 2016;44:1515-22.
13. Kalhan R, Mikkelsen M, Dedhiya P, et al. Underuse of lung protective ventilation: analysis of potential factors to explain physician behavior. Crit Care Med 2006;34:300-6.
14. Mikkelsen ME, Dedhiya PM, Kalhan R, Gallop RJ, Lanken PN, Fuchs BD. Potential reasons why physicians underuse lung-protective ventilation: a retrospective cohort study using physician documentation. Respiratory Care 2008;53:455-61.
15. Rubenfeld GD, Cooper C, Carter G, Thompson BT, Hudson LD. Barriers to providing lung-protective ventilation to patients with acute lung injury. Crit Care Med 2004;32:1289-93.
16. Dennison CR, Mendez-Tellez PA, Wang W, Pronovost PJ, Needham DM. Barriers to low tidal volume ventilation in acute respiratory distress syndrome: survey development, validation, and results. Crit Care Med 2007;35:2747-54.
17. Weiss CH, Baker DW, Tulas K, et al. A Critical Care Clinician Survey Comparing Attitudes and Perceived Barriers to Low Tidal Volume Ventilation with Actual Practice. Ann Am Thoracic Soc 2017;14:1682-9.
18. Sjoding MW, Cooke CR, Iwashyna TJ, Hofer TP. Acute Respiratory Distress Syndrome Measurement Error. Potential Effect on Clinical Study Results. Ann Am Thoracic Soc 2016;13:1123-8.
19. Sjoding MW, Hofer TP, Courey A, Cooke CR, Iwashyna TJ. Interobserver Reliability of the Berlin ARDS Definition and Strategies to Improve the Reliability of ARDS Diagnosis. Chest 2017.
20. Kahn JM, Andersson L, Karir V, Polissar NL, Neff MJ, Rubenfeld GD. Low tidal volume ventilation does not increase sedation use in patients with acute lung injury. Crit Care Med 2005;33:766-71.
21. Serpa Neto A, Simonis FD, Barbas CS, et al. Association between tidal volume size, duration of ventilation, and sedation needs in patients without acute respiratory distress syndrome: an individual patient data meta-analysis. Intensive Care Med 2014;40:950-7.
22. Serpa Neto A, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcome

23. Campbell MJ and Walter SJ. How to design, analyse and report cluster randomised trials in medicine and health related research: John Wiley; 2014.