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Parallel Pilot Trials of Screening Frequency for Liberation from Mechanical Ventilation the RELEASE Trial and SENIOR Trial Protocols

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Abstract

Rationale: Reducing the duration of invasive ventilation is a priority in the intensive care unit (ICU). Once daily screening to identify candidates for spontaneous breathing trials (SBTs) is poorly aligned with the continuous care ICU environment.

Objectives: The primary objective of the pilot randomized RELEASE and SENIOR trials is to assess our ability to recruit 50 non-elderly (<65 years) and 100 elderly (≥ 65 years) critically ill adults into parallel trials comparing once vs at least twice daily screening. Secondary objectives are to evaluate clinicians' adherence to the screening protocols, assess current practices related to management of sedation, analgesia, delirium and patient mobilization before screening assessments, identify barriers to enrollment, characterize trial participants based on weaning difficulty, and obtain preliminary estimates of the alternative screening strategies on clinical outcomes. In the SENIOR trial, we will also compare recruitment metrics and intervention effect between elderly (65 to 80 years) and very elderly (>80 years) participants.

Methods: In both trials, we will enroll critically ill adults receiving invasive ventilation for at least 24 hours who can initiate or trigger breaths. In both arms, Respiratory Therapists (RTs) will screen patients between 06:00 and 08:00 hours daily to identify SBT candidates. In the 'at least twice daily screening' arm, RTs will also screen patients between 13:00 and 15:00 hours with additional screening periods permitted at clinicians' discretion. We will consider the studies feasible if we can recruit on average, 1 to 2 patients per month per ICU and attain at least 80% protocol adherence.

Relevance: Screening patients more frequently and conducting more frequent SBTs has the potential to reduce the duration of time spent on invasive ventilation and in the ICU. Information garnered from these pilot randomized trials will inform the design of a large, future trial.

Clinical trial study: The RELEASE Trial ClinicalTrials.gov Identifier: NCT02001220; The SENIOR Trial

ClinicalTrials.gov Identifier: NCT02243449

Keywords: Screening; Weaning; Critical care; Randomized controlled trials; Elderly

Background

Weaning is the process in which the work of breathing is transferred from the ventilator back to the patient and mechanical ventilation is gradually or abruptly withdrawn. Approximately 40% of the total time spent on mechanical ventilation is dedicated to weaning [1]. Limiting the duration of invasive ventilation is a research priority in critical care [2]. Prolonged invasive ventilation is a key factor driving intensive care unit (ICU) costs and is associated with the development of intubation-related complications including ventilator associated pneumonia (VAP) [3], sinusitis [4] and respiratory muscle weakness [3]. VAP, in turn, is associated with an attributable increase in ICU length of stay and a trend toward increased mortality [5].

Compelling research supports use of specific strategies to limit the duration of invasive ventilation and improve clinically important outcomes including (i) early identification of weaning candidates using screening protocols [6-8], (ii) tests of patients' ability to breathe spontaneously [i.e., spontaneous breathing trials (SBTs)] [9-11] and (iii) the use of selected ventilator modes or strategies [Pressure Support (PS) and SBTs (using PS or T-piece)] [12-14]. The use of once daily SBTs as a weaning strategy in patients who require serial SBTs is based on a small number of trials including few patients [12,13]. A meta-analysis of 17 trials (n=2,434) supports the use of screening protocols to identify candidates for SBTs [15]. Most trials in this review compared

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once daily screening to usual care which either required a physician order to conduct an SBT or was not described. Observational data by our group supports that once daily screening is the current standard of care nationally and internationally [16,17]. However, no randomized trial has compared a strategy of more frequent screening to once daily screening to identify SBT candidates. Given that respiratory therapists (RTs) are available around the clock in North American ICUs, a significant opportunity exists to screen patients more frequently, conduct more frequent SBTs, and reduce the time spent on invasive ventilation and in the ICU.

Individuals who are at least 65 years of age represent 13% of the population, and account for 44% of Canadian health care spending [18]. In a multicenter study conducted in 1990, Rockwood and colleagues found that patients 65 years and over constitute 26% to 51% of ICU admissions [19]. With the aging baby boomer cohort, the elderly are expected to comprise 23% of the population by 2031 [20]. Most studies support that older patients, especially those over 80 years have increased ICU [21,22] and hospital mortality [23-28]. Notwithstanding, life support technologies are routinely used today to extend life, regardless of age, and discussions about level of care and mechanical ventilation discontinuation typically occur only after intubation has occurred. Only one mechanical ventilation trial [29] and no weaning trials have been conducted in the elderly. Consequently, uncertainty exist regarding the generalizability of current evidence to elderly patients amidst more frequent comorbidities, increased frailty and malnutrition, their potential to fatigue during weaning and to be excluded from trial participation due to treatment limitations.

Pilot Screening Trial Objectives

The RELEASE Trial (<65 years, n=50) and the SENIOR Trial (≥ 65 years, n=100) are two pilot multicenter RCTs which will compare two screening strategies to identify weaning candidates (once daily vs. at least twice daily screening) in 12 Canadian ICUs. The primary objective of these pilot trials is to assess our ability to recruit the desired population. The secondary objectives are to (i) evaluate clinician's ability to adhere to the screening protocols, (ii) assess current practices in sedation, analgesia and delirium management and timing of patient mobilization before conducting screening assessments, (iii) identify barriers (clinician, institutional) to enrolling patients, (v) characterize trial participants based on weaning difficulty, and (v) obtain preliminary estimates of the effect of the alternative screening strategies on clinical outcomes. In the SENIOR trial we will compare recruitment and effects of the interventions between elderly (65 to 80 years) and very elderly (>80 years) participants (Table 1). Information garnered from these trials will inform the design of a future large screening trial.

Study Population

With the exception of age, both trials have identical inclusion and exclusion criteria. We will include:

(i) critically ill adults (<65 years in RELEASE and ≥ 65 years in SENIOR) receiving invasive mechanical ventilation for at least 24 hours, (ii) capable of initiating spontaneous breaths on Pressure Support (PS) or Proportional Assist Ventilation (PAV), or triggering breaths on volume or pressure assist control (AC), volume or pressure Synchronized Intermittent Mandatory Ventilation (SIMV) ± PS, Pressure Regulated Volume Control (PRVC), Volume Support (VS) or Airway Pressure Release Ventilation (APRV), (iii) fractional concentration of inspired oxygen (FiO_2) ≤ 0.70 and (v) positive end-expiratory pressure (PEEP) of ≤ 12 cm H_2O. We present the trial exclusion criteria in Table 2.

Study Randomization

Research personnel (research coordinators and/or RTs) will identify,

Release Trial	Senior Trial
Primary Objective [1] To assess the feasibility of recruiting critically ill adults breathing spontaneously on pressure support (PS) or proportional assist ventilation (PAV) triggering breaths on volume or pressure assist control (AC), volume or pressure synchronized intermittent mandatory ventilation (SIMV) ± PS, pressure regulated volume control (PRVC), volume support (VS), or airway pressure release ventilation (APRV) into a trial comparing 'once daily' to 'at least twice daily' screening to identify weaning candidates.	**Primary Objective** [1] Assess the feasibility of recruiting invasively ventilated elderly (age ≥ 65 years) critically ill adults into a weaning trial comparing alternative screening strategies
Secondary Objectives [2] Evaluate clinician compliance with 'once daily' versus 'at least twice daily' screening assessments and the potential for contamination in the 'once daily' arm, [3] Assess current practices related to sedation, analgesia and delirium management, and mobilization before conducting 'once daily' or 'at least twice daily screening' assessments of weaning readiness to quantify potential factors that may lead to performance bias in the future, planned, large scale weaning trial [4] Identify barriers (clinician and institutional) to recruitment into this study.	**Secondary Objective** [2] Evaluate clinician adherence to the assigned screening protocols in both study arms.
Tertiary Objectives [5] Classify trial participants as requiring (i) simple, (ii) difficult or (iii) prolonged weaning using the 'Task Force on Weaning' definitions [34]. [6] Obtain preliminary estimates of the impact of the alternative screening strategies ('once daily' vs. 'at least twice daily'') on clinically important outcomes [e.g., time to first spontaneous breathing trial (SBT) and first successful SBT, time to first extubation and successful extubation, total duration of mechanical ventilation, intensive care unit (ICU) and hospital length of stay, ICU and hospital mortality, use of noninvasive ventilation (NIV) following extubation, complications (self-extubation, tracheostomy, reintubation, proportion requiring prolonged mechanical ventilation) and adverse events.	**Tertiary Objectives** [3] Compare the proportions of enrolled elderly and very elderly trial participants. [4] Compare the proportions of consents obtained and declined for trial participation similar between *eligible* elderly and very elderly trial participants. [5] Compare rates and reasons for trial exclusion based between eligible elderly and very elderly patients. [6] Compare the effect, in preliminary estimates, do the alternative screening strategies have on clinically important outcomes[e.g., time to first spontaneous breathing trial (SBT) and first successful SBT, time to first extubation and successful extubation (Appendix 2), total duration of mechanical ventilation, intensive care unit (ICU) and hospital length of stay, ICU and hospital mortality, use of noninvasive ventilation (NIV) following extubation, complications (self-extubation, tracheostomy, reintubation, proportion requiring prolonged mechanical ventilation) and adverse events] between elderly and very elderly trial participants.
	Quaternary Objectives [7] Assess and quantify current practices related to sedation, analgesia an delirium management and mobilization before conducting 'once daily' or 'at least twice daily screening' assessments of weaning readiness with the goal of quantifying factors that may lead to performance bias in the future, planned, large scale weaning trial. [8] Identify barriers (clinician and institutional) to recruitment into this study. [9] Classify trial participants as requiring (i) simple, (ii) difficult or (iii) prolonged weaning using the 'Task Force on Weaning' [34] definitions.

Table 1: Objectives of the release and senior trials.

Excluded patients will include:
(1) Admitted after cardiopulmonary arrest or with brain death or expected brain death,
(2) Evidence of myocardial ischemia in the 24 hour period before enrollment,
(3) Receiving continuous invasive mechanical ventilation for ≥ 2 weeks,
(4) Tracheostomy in situ at the time of screening,
(5) Receiving sedative infusions for seizures or alcohol withdrawal,
(6) Require escalating doses of sedative agents,
(7) Receiving neuromuscular blockers or who have known quadriplegia, paraplegia or 4 limb weakness or paralysis preventing active mobilization (e.g., active range of motion, exercises in bed, sitting at edge of bed, transferring from bed to chair, standing, marching in place, ambulating),
(8) Moribund (e.g., at imminent risk for death) or who have limitations of treatment (e.g., withdrawal of support, do not reintubate order, however, do not resuscitate orders will be permitted),
(9) Profound neurologic deficits (e.g. large intracranial stroke or bleed) or Glasgow Coma Scale (GCS) ≤ 6,
(10) Using modes that automate SBT conduct,
(11) Currently enrolled in a confounding study that includes a weaning protocol,
(12) Previously enrolled in this trial
(13) Already undergone an SBT or are on T-piece, or CPAP alone (without PS), or PS ≤ 8 cm H_2O regardless of PEEP, or other 'SBT equivalent' settings immediately before randomization,
(14) Already undergone extubation [planned, unplanned (e.g. self, accidental)] during the same ICU admission.

Table 2: Exclusion criteria in the release and senior trials.

consent (where applicable), and enroll eligible patients from Monday to Friday using the web-based randomization system within the Research Electronic Data Capture (RedCap, Vanderbilt, USA) system developed for each trial. Eligible patients will be randomly assigned 1:1 to once or at least twice daily screening using a central randomization system with variable undisclosed block sizes to ensure allocation concealment. In both trials, randomization will be stratified by ICU and in the SENIOR trial by age (elderly vs. very elderly). Given the minimal risk associated with the study interventions, the narrow time window for inclusion, and our desire to limit selection bias, we proposed use of a hybrid consent model that prioritizes patient or substitute decision maker consent when feasible but allows deferred consent (consent post-randomization) in their absence. Individual research ethics boards of participating ICUs will review and approve consent models for trial participation.

Study Interventions

Screening for SBT candidates

After randomization, RTs and bedside registered nurses (RNs) in participating ICUs will be informed of the allocated study arm. In the 'once daily screening arm', RTs will screen patients daily between approximately 06:00 and 08:00 hours to identify SBT candidates. If not yet completed, RTs will prompt bedside RNs to complete the practice checklist (Table 3). In the at least twice daily screening arm, patients will also be screened for SBT readiness daily between approximately 13:00 and 15:00 hours. If a screening period is missed [inadvertently or due to an investigation or intervention (operation/procedure) necessitating patient absence from the ICU], it may be conducted later on the same day, ideally within 6 hours of the scheduled screening period. In the at least twice daily screening arm, additional screening periods will be permitted at clinician (RT and physician) discretion.

Bedside nurses will record data related to other interventions in use to assess whether patients are being optimized for weaning or the conduct of SBTs. These checklists will assist in determining the need to protocolize approaches to sedation, analgesia, delirium management and the time of mobilization in the future planned trial. When patients pass a screening assessment, an SBT will be conducted. If the SBT is successful, patients will be assessed for extubation criteria. Extubation will be performed according to clinician guidance and local guidelines. We will not direct the time of extubation, rather we will record the time to successful SBT completion, the time when all extubation criteria are met (Appendix 1), and the date and time of actual extubation to inform the design of the future, large RCT.

1C. Immediately prior to SBT screening, were sedative agents (infusions or intermittent doses) being titrated to: a target SAS of 3 to 4 or RASS of 0 to -3? e.g., Lorazepam (Ativan), Midazolam (Versed), Diazepam (Valium), Propofol (Diprivan)	☐ Yes ☐ No ☐ Not Receiving Sedatives
1D. Immediately prior to SBT screening, were analgesic agents (infusions or intermittent doses) being titrated to the patients' comfort, level of arousal, or a pain scale? e.g., Morphine, Meperidine (Demerol), Fentanyl (Sublimaze),Fentanyl patch (transdermal), Hydromorphone (Dilaudid), Dexmetitomidine (Precedex)	☐ Yes ☐ No ☐ Not Receiving Analgesics
1E. Immediately prior to SBT screening, was the patient receiving medications to prevent or treat delirium? e.g., Resperidone (Respirdal), Loxapine (loxitane), Haldoperidol (Haldol,Serenase), Buspirone (Buspar), Buproprion (Wellbutrin), Lithium (Eskalith, Lithobid), Quetiapine (Seroquel), Olanzepine (Zyprexa), Dexmeditomidine (Precedex), Donepezil (Aricept), Gabapentin (Neurontin)	☐ Yes ☐ No ☐ Not Delirious (not receiving delirium medications)
1F. Prior to this SBT screening was the patient being mobilized by a health care team member or family? (Indicate highest level of mobilization) ACTIVE=Exercises in bed/active range of motion, biking (active and passive, or active only),sitting at edge of bed, transferring from bed to chair (Without standing), standing, transferring from bed to chair (With standing), marching in place, ambulation, PASSIVE=Cardiorespiratory therapy/chest physiotherapy, nothing (lying in bed)/passive range of motion, biking (passive only)	☐ Yes (Active) ☐ Yes (Passive) ☐ Not being mobilized passively or actively

Table 3: Practice checklist.

To pass the screening assessment and undergo an SBT, all of the following criteria must be met:

1. Patient must be capable of initiating spontaneous breaths on PS or PAV, or triggering breaths on volume or pressure AC, volume or pressure SIMV ± PS, PRVC, VS or APRV,
2. Ratio of partial pressure of oxygen to FiO_2 (PaO_2/FiO_2) ≥ 200 mm Hg,
3. Respiratory Rate ≤ 35 breaths/min,
4. PEEP ≤ 10 cm H_2O,
5. Heart Rate ≤ 140 beats/min,
6. Ratio of respiratory frequency to tidal volume (f/V_T)<105 breaths/min/L during a 2 minute assessment on CPAP of 0 cm H_2O (alternatively PS 0 cm H_2O+PEEP 0 cm H_2O).

For patients rested on controlled modes of ventilation at night, RTs will assess for these criteria on the 'daytime' mode of ventilation.

Conduct of SBTs

Initial and subsequent SBTs will be 30 -120 minutes in duration and may be conducted with any one of the following techniques: T-piece, CPAP ≤ to 5 cm H_2 O or PS ≤ 8 cm H_2 O with PEEP ≤ 5–10 cm H_2O. Higher levels of PEEP (8-10 cm H_2O) will be permitted (and recorded) to allow for clinician discretion in conducting SBTs in specific patients (e.g., obese, chronic obstructive pulmonary disease). Each centre will choose one technique for all patients enrolled in the pilot trial. Between SBTs, patients will be returned to the mode of ventilation used before the SBT, unless criteria are met to remain on or return to a mode of support that assumes no spontaneous or triggered breaths.

We will record the ventilator settings before SBTs, the duration and settings used to conduct SBTs, and the type of humidification used during SBTs on daily case report forms to ascertain what clinicians do in practice and evaluate the need for SBT standardization of SBT practice in the future trial. In both groups, patients who pass an SBT will be assessed for extubation criteria. Criteria for SBT failure and to remain on or return to a fully controlled/supported mode of ventilation are presented in Appendix 1. Patients who meet the latter criteria will be reassessed daily to identify the earliest time when they meet initial inclusion criteria and can initiate spontaneous breaths or trigger breaths on specified modes. When enrolment criteria are met, the protocol can be resumed according to initial treatment assignment. If patients can breathe spontaneously or trigger breaths on specified modes before 10:00 am, the allocated screening protocol can resume. However, if this criterion is not met until after 10:00 am, screening will be conducted once daily in both treatment arms and as per treatment allocation thereafter. Practices checklist assessments will not be mandatory while patients remain on a fully controlled mode.

Extubation

Extubation will be performed according to clinician guidance and local guidelines. Rather than impose timing of extubation in these pilot RCTs, we will observe the time to passing an SBT, meeting all extubation criteria, and the date and time of actual extubation to inform the design of the larger, planned RCT. All of the above criteria (except #4 and #5) will similarly apply to patients who undergo tracheostomy mask trials and are disconnected from mechanical support. All intubated patients will be assessed for extubation after successful completion of an SBT. We will pilot selected extubation criteria during the feasibility trials (Appendix 1).

Other important considerations (Use of Noninvasive Ventilation, Reintubation and Tracheostomy)

Additional important considerations in conducting these trials include (i) the use of non-invasive ventilation after extubation and (ii) criteria for reintubation (Appendix 2). Patients can be extubated to NIV to facilitate weaning. All patients requiring reintubation after successful extubation (Appendix 2) will be ventilated according to usual practice and at the discretion of the clinical team. If patients are reintubated within 48 hours after extubation, they will be reassessed daily to identify the earliest time when they can initiate spontaneous breaths or trigger breaths on selected modes and when they meet study initial inclusion criteria once again so that screening for SBT readiness can resume. Patients will remain in the same group to which they were originally randomized. For all enrolled patients, the screening protocols will be followed until ICU discharge, ICU death, successful extubation (Appendix 2), or until day 60 (deemed ventilator dependent) after randomization. All patients will be followed until successful extubation, ICU discharge, ICU death, or until day 60 (deemed ventilator dependent) after randomization. Approaches to titration of ventilator settings, PEEP, and FiO_2 in both arms are detailed in Appendix 2.

Patients who do not have a tracheostomy at study inclusion may undergo tracheostomy later. We will request in both groups that investigators, when possible, wait until at least day 10 before considering an elective tracheostomy. Physicians may offer tracheostomy earlier if it is not an elective procedure (e.g., fixed airway obstruction) and in consultation with the site investigator. Guidance on timing of tracheostomy and weaning in patients who undergo tracheostomy are provided in Appendix 2 [30]. In the event that patients receive a tracheostomy, once or twice daily screening will cease, but patients should remain in the study until liberated (successful disconnection) (Appendix 2).

Study Outcomes

Regarding the primary and secondary outcomes of both the RELEASE and SENIOR Trials, we will consider the study feasible if we can (i) recruit, on average, 2 invasively ventilated, critically ill patients per ICU per month in each study and (ii) adhere to protocols in at least 80% of trial participants in both study arms. We expect contamination (more frequent screening) in the once daily screening arm will be ≤ 10% and that sedation, analgesia, delirium management and mobilization practices will be recorded ≥ 80% of the time, when feasible. Management strategies (sedation, analgesia, delirium, mobilization) utilized in < 60% of assessments in either arm will be considered potentially important.

In both pilot trials, we expect to identify clinician and institutional barriers to recruitment. We will also estimate the proportion of patients who can be extubated after a first SBT (simple weaning) [31] to inform future sample size estimates. In the SENIOR Trial we will elucidate whether differences exist in the proportion of elderly and very elderly critically ill patients who are excluded, consented, and ultimately enrolled. We will obtain preliminary estimates of the effect of the screening strategies on important clinical outcomes. Successful extubation will be defined as the time when unsupported, spontaneous breathing began and was sustained for ≥ 48 hours after extubation (or disconnection from the ventilator for patients who have a tracheostomy).

Statistical Analyses and Sample Size Estimation

Descriptive statistics including means, standard deviations, medians, interquartile ranges and frequency distributions will be used

to summarize the data. For the primary analysis, we will report the number of patients included in the trials. In secondary analyses, we will evaluate compliance with the assigned screening strategy by evaluating whether a single screening assessment was completed in the 'once daily screening' arm (yes/no) and whether two or more assessments were conducted in the 'at least twice daily screening' arm (yes/no) among elderly and very elderly participants in each arm. We will exclude circumstances when it was not feasible to conduct assessments from this computation (e.g. patient not in the ICU, met criteria to return to an alternate mode of ventilation without spontaneous or triggered breaths, etc.). A screening compliance rate of $\geq$ 80% and a contamination rate of $\leq$ 10% (once daily arm) will be considered acceptable. Approaches to analyzing additional outcomes are detailed in Appendix 3.

To enable participating centres to become familiar with implementing both screening strategies and to ascertain feasibility endpoints, we estimate that 100 elderly critically ill patients will be required in the SENIOR Trial and 50 patients in the RELEASE Trial. In the SENIOR trial, a sample size of 100 patients will enable us to detect 80% protocol adherence with 95% confidence interval (CI) of 71.1% to 86.7%. The lower limit of the 95% CI would be the minimum protocol adherence rate that we would consider acceptable for a larger planned trial. To ensure that all ICUs gain some experience with both protocols, we will set a maximum site enrolment of 18 patients per ICU in the RELEASE trial and 35 patients per ICU in the SENIOR trial.

Discussion

Timely liberation from invasive ventilation has the potential to minimize critically ill patient's exposure to invasive ventilation and improve clinical outcomes. Although once daily screening is the most common current practice, it is not well aligned with the continuous care paradigm of the ICU and disregards the potential impact of management decisions made after the first screen. Both trials test a simple construct: more frequent screening will result in earlier identification of weaning candidates, more frequent SBTs, and less time spent on mechanical ventilation and in the ICU. Additionally, more frequent SBTs may provide incremental information to clinicians to increase their confidence in extubation decision-making. With RTs available around the clock in Canadian teaching hospitals, these trials offer a unique opportunity to clarify the optimal screening frequency. We encountered several challenges in designing these trials including identifying the population of interest, selecting the control screening strategy, deciding how to conduct SBTs and manage cointerventions, and selecting relevant outcomes.

Running the pilot trials in parallel will enable us to utilize the same trial infrastructure to address theoretical concerns related to the study population. In the SENIOR trial, we will determine whether more frequent SBTs induce fatigue (manifested as SBT failure) in the very elderly, especially the frail very elderly, compared to elderly trial participants. We will also assess whether reasons for trial exclusion and consent rates differ between elderly and very elderly trial participants. Mechanical ventilation trials typically exclude patients who have treatment limitations and specific comorbid illnesses, both of which may be more prevalent in the very elderly and thus may limit enrollment. Different consent and exclusion rates could prolong recruitment, influence the duration of a future planned trial, and affect the generalizability of its results.

Most screening RCTs have compared a strategy of once daily screening typically led by allied health care providers to usual care, often requiring a physician order to conduct SBTs. A systematic review and meta-analysis of 17 trials involving 2,434 patients demonstrated that screening protocols were associated with a 26% reduction in total duration of mechanical ventilation [n=14 trials, 95% CI (13% - 37%), p=0.0002], 70% reduction in weaning time [n=8 trials, 95% (CI 27% - 88%), p=0.009] and an 11% reduction in ICU stay [n=9 trials, 95% CI (3% - 19%), p=0.01] [15]. In this systematic review, 12 trials did not describe usual care and only one trial (n=385) compared twice daily screening, led by RTs and bedside nurses, to usual care and found reduced duration of ventilation and incidence of VAP favoring twice daily screening [8]. These findings together with those of national and international weaning surveys support use of once daily screening as the control strategy and the need to evaluate the impact of more frequent screening [15-17]. A priori, we anticipate that it will be more challenging to demonstrate benefit of more frequent screening compared to once daily screening versus usual care.

We considered several issues in designing the study intervention. First, our objective was to evaluate the merits of screening frequency and not SBT conduct itself. Notwithstanding, we recognized that the objective of screening is to identify SBT candidates and the outcome of interest is SBT success or failure. Second, we acknowledged that there is considerable practice variation exists in how clinicians conduct SBTs [16,17]. Third, while the Task Force on Weaning supports conduct of SBTs with either T-piece or low levels of PS with or without positive end expiratory pressure of 30 minutes duration in adults, this document is not a clinical practice guideline [31]. Fourth, a recent Cochrane Review of 9 trials found no difference between PS and T-piece on weaning success (RR 1.07, 95% CI 0.97 to 1.17, 9 studies), ICU mortality (RR 0.81, 95% CI 0.53 to 1.23, 5 studies), reintubation (RR 0.92, 95% CI 0.66 to 1.26, 7 studies), ICU and long-term weaning unit length of stay (MD -7.08 days, 95% CI -16.26 to 2.1, 2 studies), and pneumonia (RR 0.67, 95% CI 0.08 to 5.85, 2 studies) [32]. Only 4 trials in this review directly compared PS to T-piece SBTs. The pooled results support that compared to T-piece SBTs, patients who underwent PS SBTs were more likely to be successful (RR 1.09, 95% CI 1.02-1.17). In the absence of an equivalency trial directly comparing the alternative SBT techniques and with demonstrated practice variation in SBT conduct [17], we standardized SBT conduct within participating ICUs but not among ICUs. The SBT technique most commonly used within participating ICUs will be utilized for SBTs in trial participants. Allowing for between-site variation SBT conduct, we excluded patients who had already undergone an SBT and clarified this to include those on SBT equivalent settings (Table 2).

Duration of weaning may be influenced by several practices including titration of sedation and analgesia, delirium management, and timing of mobilization in invasively ventilated patients. Current evidence favors use of protocol by bedside nurses to titrate sedation to a target score [33] without daily interruption of sedative infusions [34,35]. Although prospective trials of delirium prevention and treatment remain limited, it is known that delirious patients have worse clinical outcomes [36]. The inferences that can be made are limited by inconsistent application of non-pharmacologic prevention strategies, lack of placebo control, and limited reporting of important clinical outcomes [36]. Early mobilization can limit ICU-acquired complications and reduce the duration of ventilation; ICU and hospital stay, days of delirium, and improve physical function at hospital discharge [37,38]. Invasively ventilated adults are often physically inactive, resulting in skeletal muscle atrophy and weakness, which may affect weaning. Although sedation, analgesia, and antipsychotic administration, and mobilization are potential cointerventions, their impact on SBT frequency and timing are largely unknown. In necessarily unblinded weaning trials, these co-

interventions may be applied differently between arms and threaten study validity. To address this concern, we document each of these practices by using practice checklists. Interventions that are not utilized or utilized with different frequency between treatment arms may be candidates for protocolization or detailed quantification in a future trial.

Finally, we aimed to select outcomes that are relevant to the weaning process. Outcomes including time to first SBT, time to first successful SBT, time to first successful extubation, weaning time, extubation outcome, and ICU length of stay are clinically important and relevant. More frequent screening may not directly affect extubation which involves assessment of other factors such as cough strength, ability to manage secretions, level of consciousness and presence of a cuff leak. Although time to extubation and successful extubation are considered to be clinically important, they are confounded by factors related to extubation readiness and may not directly reflect screening frequency. Although, time to first SBT or time to first successful SBT may better reflect the intervention of interest, the impact of screening frequency on the process of weaning and extubation remains to be determined.

Conclusion

The proposed trials aim to identify the optimal screening frequency to liberate critically ill patients from invasive ventilation. At least twice daily screening has the potential to improve both patient outcomes and resource utilization. Information garnered from these pilot trials will inform the design of a large future trial to address this issue rigorously and comprehensively.

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