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Liberation from mechanical ventilation using Extubation Advisor Decision Support (LEADS): protocol for a multicentre pilot trial

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ABSTRACT

Introduction Timely successful liberation from invasive ventilation has the potential to minimise critically ill patients' exposure to invasive ventilation, save costs and improve outcomes; yet no trials have evaluated strategies to better inform extubation decision-making. The Liberation from mechanical ventilation using Extubation Advisor (EA) Decision Support (LEADS) Pilot Trial will assess the feasibility of a trial of a novel extubation decision support tool on feasibility metrics. The primary feasibility outcome will reflect our ability to recruit the desired population. Secondary feasibility outcomes will assess rates of (1) consent, (2) randomisation, (3) intervention adherence, (4) bidirectional crossovers and the (5) completeness of clinical outcomes collected. We will also evaluate physicians' perceptions of the usefulness of the EA tool and measure costs related to EA implementation.

Methods and analysis We will include critically ill adults who are invasively ventilated for ≥48 hours and who are ready to undergo a spontaneous breathing trial (SBT) with a view to extubation. Patients in the intervention arm will undergo an EA assessment that measures respiratory rate variability to derive an estimate of extubation readiness. Treating clinicians (respiratory therapists, attending physicians and intensive care unit fellows) will receive an EA report for each SBT conducted. The EA report will assist, rather than direct, extubation decision-making. Patients in the control arm will receive standard care. SBTs will be directed by clinicians, using current best evidence, without EA assessments or reports. We aim to recruit 1 to 2 patients/month in approximately 10 centres, and to achieve >75% consent rate, >95% randomisation among consented patients, >80% of EA reports generated and delivered (intervention arm), <10% crossovers (both arms) and >90% of patients with complete clinical outcomes. We will also report physician point-of-care perceptions of the usefulness of the EA tool.

Ethics and dissemination The LEADS Pilot Trial is approved by the Research Ethics Boards of all participating centres and Clinical Trials Ontario (4008). We will disseminate the LEADS trial findings through conference presentations and publication.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This protocol described a novel open-label 10-centre randomised controlled trial of the extubation advisor (EA) decision support tool and usual care to aid in extubation decision-making in critically ill patients.
⇒ The EA tool estimates an individual patients' risk for extubation failure based on (1) the individual patient's respiratory rate variability (RRV) during a spontaneous breathing trial (SBT), (2) a standardised extubation readiness checklist, and (3) individualised extubation failure risk mitigation strategies and synthesises the prediction of extubation failure in an EA report.
⇒ The primary outcome will reflect our ability to enrol patients overall and at participating centres. Secondary feasibility outcomes will reflect our ability to consent, randomise, collect complete outcomes data, adhere to the intervention protocols (EA and standard care) and limit crossovers. We will also assess the perceived usefulness of EA reports to physicians.
⇒ As a feasibility trial, the LEADS trial is the first trial to evaluate an extubation bedside decision support tool and implement a RRV-derived predictive model to better inform extubation decision-making.
⇒ By necessity, this trial is unblinded. Consequently, we adopted several strategies during protocol development to reduce bias and enhance internal validity.

Trial registration number NCT05506904. Protocol version: 24 April 2024.

INTRODUCTION

Provision of intensive care is labour and resource intensive and costly. Approximately 20 million individuals globally receive

mechanical ventilation annually.[1] Increased time on invasive mechanical ventilation markedly increases the complexity and costs of care[2] and may contribute to patient harm.[3 4] Timely and safe liberation from mechanical ventilation has been identified as a top research priority for patients and clinicians.[5 6]

Most critically ill patients undergo a trial of extubation. A failed attempt at extubation with a need for reintubation occurs in 15–20% of critically ill patients and is associated with increased mortality, intensive care unit (ICU) length of stay (LOS), costs (US$34 000 per failed extubation),[7] and the need for rehabilitation after ICU discharge.[8–16] Specifically, an economic analysis supports that a failed (vs successful) extubation results in increased ICU LOS (21 vs 10 days) and substantially increases costs of hospitalisation ($102 000 vs $51,000 CAD per patient).[17] Given the consequences and costs associated with failed attempts at extubation for patients and our healthcare system, it is imperative to improve the process of extubation and extubation decision-making. Notwithstanding, extubation is a critical, high-stakes decision as extubating patients too soon predisposes them to extubation failure and its associated complications while extubating patients too late increases patients' risk for complications related to prolonged mechanical ventilation. Recent studies have highlighted the consequences of failed extubation for COVID-19 patients and the increased risk for transmission of COVID-19 to healthcare workers during manual ventilation before intubation.[18]

Although spontaneous breathing trials (SBTs) are regarded internationally as the standard of care to assess liberation from invasive ventilation, comparatively less is known about predictors of extubation success (ie, liberation from the endotracheal tube).[6 19] SBTs are focused assessments of a patient's ability to tolerate minimal ventilatory support on low ventilator settings. In North America, SBTs are typically performed by respiratory therapists (RTs) who work collaboratively with ICU physicians to manage mechanical ventilation.[6] More than two decades of research support the use of specific strategies to limit the duration of invasive ventilation including the (1) use of multidisciplinary screening protocols to identify candidates who are ready to undergo an SBT,[20–22] (2) conduct of SBTs for patients who pass screening criteria,[23–25] and (3) specific strategies to reduce ventilator support for patients who fail an initial SBT.[26–28] Considerably less research has been conducted to identify predictors of extubation readiness (ie, cuff leak test, grip and cough strength, and the rapid shallow breathing index (RSBI)) with the RSBI regarded as the best current predictor.[29 30] However, even the RSBI has been shown to have limited value in predicting successful extubation (positive likelihood ratio: 1.49).[30–33] Extubation decision-making, a collaborative process involving the knowledge and skills of RTs and physicians with physicians ultimately making decisions regarding extubation, is poorly studied.[6] A national observational study of SBT conduct identified significant intrainstitutional and interinstitutional variation in how SBT outcomes were reported to physicians by RTs.[34] With few advances in this field over the past two decades, there is a strong need for strategies to enhance extubation decision-making and improve extubation outcomes.[35]

Although critically ill patients are monitored with continuous recording of waveforms (eg, electrocardiography (ECG), capnography, oxygen saturation, etc), these waveforms are routinely discarded in practice. This represents a missed opportunity to garner important information regarding patterns of variation (or variability) in heartbeat (interbeat) and breathing (interbreath) within individual patients. Although not appreciable to clinicians, variability may be uncovered by software analysis.[36–49] Multivariate variability analysis measures and analyses the degree and character of variation in interbeat or interbreath time intervals.[37 42 49] Whereas normal heart rate variability (HRV) and respiratory rate variability (RRV) reflect physiologic reserve and adaptability, decreased variability is associated with illness, age, reduced adaptability and increased stress.[37–39 41 50–52] For example, RRV is reduced in patients with organ failure and restrictive lung disease[53] and the degree of RRV reduction correlates with illness severity.[43] At least seven studies have demonstrated that reduced HRV and/or RRV during SBTs is associated with extubation failure.[53–59] In turn, reduced RRV has been shown to be a marker of increased stress during attempts to wean patients from invasive ventilation.[60–62] A 12-centre observational prospective study (n=721) showed that reduced RRV predicted extubation failure in a heterogeneous cohort of invasively ventilated adults using the 'Weaning and Variability Evaluation (WAVE) score'—a predictive score based on an average ensemble of logistic regression models including five measures of RRV[47] (figure 1). The WAVE score demonstrated complementary and superior predictive accuracy compared with conventionally used indices. It predicted extubation failure with a receiver operator curve area under the curve (ROC AUC) 0.69, better than the RSBI alone (ROC AUC 0.61), heart rate (ROC AUC 0.52), and respiratory rate (ROC AUC 0.63) alone.[47] When combined with RSBI (>105) and clinical judgement, the WAVE score improved sensitivity and positive predictive capacity (ROC AUC 0.82 and 0.87).[47]

To innovate extubation decision-making, we developed the extubation advisor (EA) tool as a clinical decision support tool. The EA tool estimates individual patients' risk for extubation failure based on (1) individual patient's RRV during an SBT (WAVE score), (2) a standardised extubation readiness checklist, and (3) individualised extubation failure risk mitigation strategies and synthesises the prediction of extubation failure in an EA report. EA reports, in turn, provide a mechanism to enhance communication between RTs and physicians regarding patients' readiness for extubation.

The primary objective of the LEADS trial is to evaluate the rate of patient enrolment overall and per centre per month. In secondary objectives, we will evaluate rates of

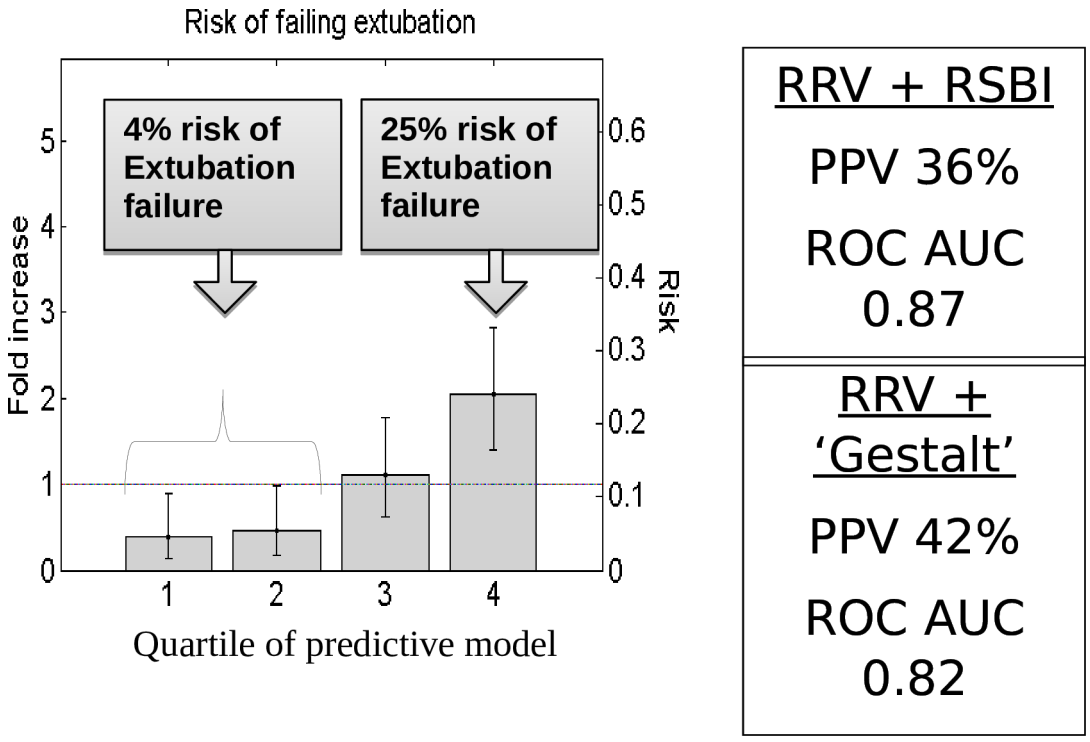

Figure 1 Risk for extubation failure based on predictive model quartile. PPV, positive predictive value; ROC AUC, receiver operator curve area under the curve; RRV, respiratory rate variability; RSBI, rapid shallow breathing index.

consent, randomisation, intervention adherence, crossovers and completeness of outcomes data. We will also assess the perceived usefulness of the EA tool to physicians and measure costs related to EA implementation. We used the Standard Protocol Items: Recommendations for Interventional Trials guideline to develop our protocol.[63]

METHODS

Trial design

The LEADS pilot trial is a 10-centre, 100-patient, concealed open-label parallel group RCT. After informed consent, research personnel will randomise patients to the EA tool or usual care.

Trial population and settings

We will include adult patients (≥18 years of age) with or without COVID-19 in the ICU who have received invasive ventilation for ≥48 hours and who are expected to undergo an initial SBT within the next 24 hours with a view to extubation as per treating physicians in 10 Canadian ICUs. An SBT will be defined as a focused assessment on low ventilator settings (T-piece, continuous positive airway pressure, or pressure support (PS) ≤8 cm H_2O regardless of positive end-expiratory pressure).[64] The trial exclusion criteria are provided in Box 1.[65]

Trial recruitment and randomisation

Research personnel (research coordinators (RCs) will identify, consent (where applicable) (online supplement 1) and enrol eligible patients from Monday to Friday, unless otherwise permitted, using the web-based randomisation system within the Research Electronic Data Capture (REDCap, Vanderbilt, USA). Since SBTs are part of standard care and recruitment is time sensitive, we will enrol patients using a hybrid consent model—prioritising first party consent (patient or substitute decision maker (SDM)) where possible and using deferred consent (for patients who lack decision-making capacity and for whom SDMs are not available).[64 66] Enrolled patients will be randomly assigned 1:1 to either EA or standard care using a central randomisation system with variable undisclosed block sizes. Randomisation will be stratified by ICU.

Trial interventions and comparators

Patients in both arms will undergo SBTs (technique, duration) as directed by clinicians. In both arms, we will recommend the use of once daily screening and T-piece

Box 1 Reasons for exclusion

We will exclude patients who:

1. Suffer from known or suspected peripheral severe myopathy or neuropathy, or limb weakness or paralysis or central (eg, post-arrest, large intracranial stroke or bleed) injury or Glasgow Coma Scale (GCS) < 6;[65]
2. Do not wish to be reintubated as part of their treatment goals;
3. Were previously extubated during the same ICU admission;
4. Have undergone one or more SBTs;
5. Already have a tracheostomy;
6. Are moribund or expected to die.

or PS SBTs for at least 30 (30–120) minutes at clinician's discretion.

Standard care arm

Based on current guidelines, we recommend once daily screening and will define an SBT as a focused assessment on low levels of ventilator support (eg, T-piece, or PS ≤8 cm H_2O) for at least 30 (30-120) minutes.[67 68] SBTs may be repeated at clinicians' discretion. The cable used to harvest data from monitors in the intervention arm will not be connected for patients in the standard care arm.

Extubation advisor arm

Patients in the intervention arm will be connected to a bedside or portable monitor displaying ECG, capnography and other waveforms. They will undergo an EA assessment during all SBTs. During capnography, a CO_2 module and tubing are connected to the endotracheal tube. A laptop with EA software will be connected to the monitor through a serial or local area network port. Waveform and vital sign data will be processed directly on the laptop. We will train RCs and RTs to harvest and record capnography waveform data during SBTs, complete extubation checklists, transmit data and interpret EA reports (online supplement 2).

The EA system will process CO_2 waveforms and vital sign data corresponding to the SBT, clean and assess data quality, compute variability metrics, and generate a score summarising the risk of extubation failure. At the end of the SBT, RTs will adjust ventilator settings as per standard practice and provide their impression of the patients' risk for extubation failure (high/average/low risk). RTs will generate reports that can display on the laptop screen or be printed for viewing. RTs will review the EA report with an ICU physician (attending or fellow) or place it at the bedside for review and extubation decision-making. An EA report will be generated for each SBT conducted until patients achieve successful extubation or other study outcome (transfer or discharge on MV, tracheostomy, death, deemed ventilator dependent (after day 45)). Physicians will be asked whether they viewed the EA report and to rate the perceived usefulness of the EA tool on a 6-point Likert scale (1—not useful to 6—very useful).[69]

Trial outcomes

Primary outcome

The primary feasibility outcome will reflect the number of patients enrolled overall and by centre from screening logs. On average, we aim to recruit one to two patients/month/centre.

Secondary outcomes

Secondary feasibility outcomes will reflect the proportion of patients consented (of those approached for consent; screening log), randomised (of all potential randomisations) and with complete outcomes. In the intervention arm, adherence will be reported as the proportion of EA reports generated, delivered and reviewed by physicians over all postrandomisation SBTs conducted. Crossovers (EA to standard care) will reflect the percentage of SBTs wherein an EA report *was not* generated, delivered or reviewed by physicians. Crossovers (standard care to EA) will reflect the percentage of SBTs wherein an EA report was inadvertently generated, delivered or reviewed by physicians in the standard care arm.

We aim to achieve >75% consent rate, >95% randomisation rate in consented patients, >80% of EA reports generated and delivered (intervention arm), <10% crossovers (both arms) and >90% of patients with complete clinical outcomes. We will report the average perceived usefulness of EA reports. Feasibility outcomes and recruitment based on COVID-19 status will be reported overall and by centre. 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 (invasively and/or non-invasively), spontaneous breathing began and was sustained for ≥48 hours after extubation (or disconnection from the ventilator for patients who have a tracheostomy). An overview of the flow through the LEADS trial is presented in figure 2 (online supplement 2).

Sample size

We will recruit 100 patients at approximately 10 participating centres over an approximate 12-month recruitment period. With 10 participating centres, personnel at each participating centre (approx. 10 patients/centre) would obtain sufficient experience in implementing the EA tool with 1:1 randomisation (approx. 5 patients in the EA arm). We estimate that 100 patients (approximately 50 in each arm) will be required to ascertain the feasibility endpoints that are the focus of the pilot trial. A sample of 100 patients will enable us to detect achievement of 80% overall protocol adherence with 95% CI (71.1% to 86.7%). Similarly, with 50 patients per arm, we will be able to detect 80% adherence in each arm with 95% CI (67.0% to 88.8%). The lower limit of the 95% CI is the minimum protocol adherence rate that would be considered acceptable for the larger trial. To ensure that all centres gain experience with the protocols, we will set a maximum site enrolment of 33 patients.

Data collection

We will track patient clinical outcomes from randomisation to hospital discharge using their electronic medical record. The site Research Coordinator will complete a short clinical outcomes case report form, which will collect the time of extubation, the outcome of extubation, the need and timing of reintubation (if present), and the need for non-invasive ventilation or high-flow nasal cannulae, all within the 72 hours post extubation. We define extubation failure as requiring reintubation within 48 hours of extubation or return to ventilator for tracheostomised patients. We will also collect the number of days the patients stay in ICU and hospital wards.

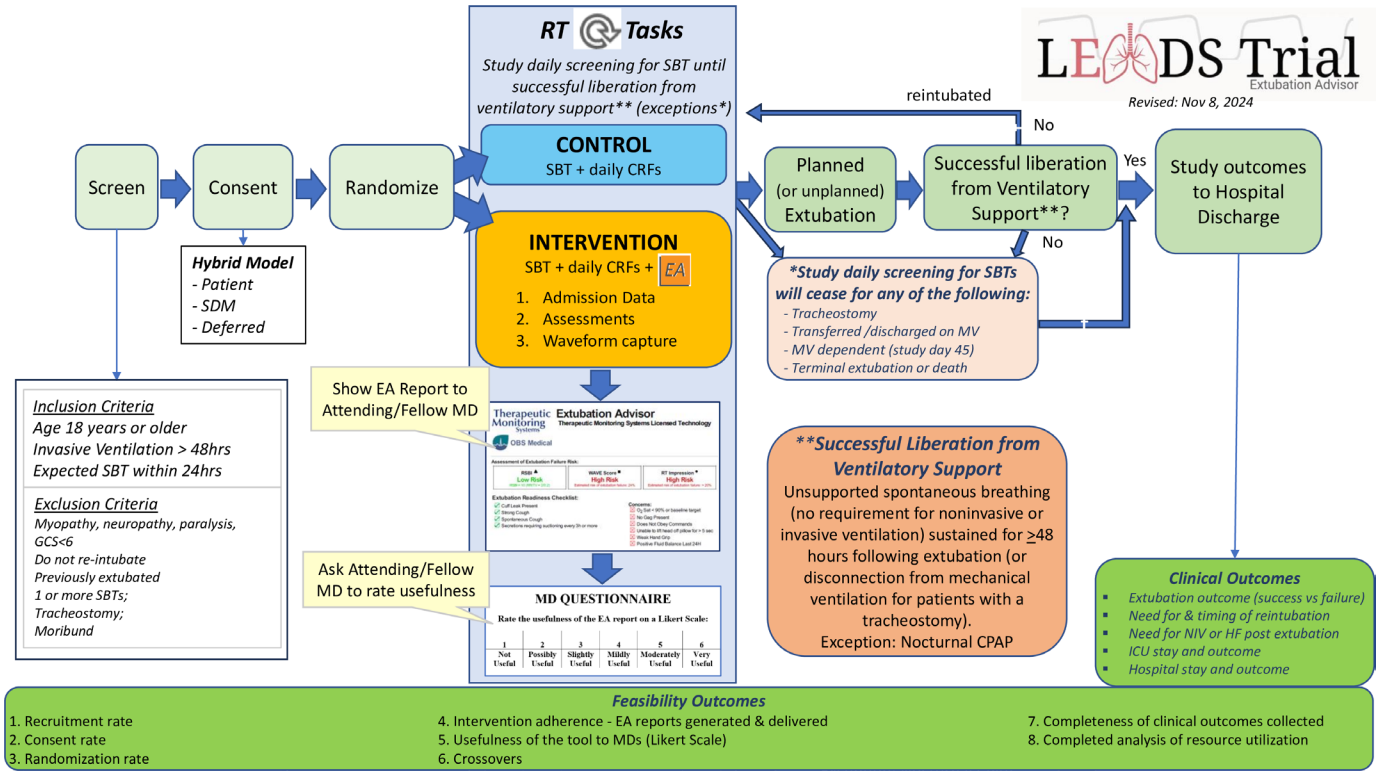

Figure 2 Flow through the LEADS trial. CRF, case report form; EA, extubation advisor; GCS; Glasgow Coma Scale; MD; physician; RT; respiratory therapist; SBT; spontaneous breathing trial; SDM; substitute decision maker.

Data collection will be deemed 'complete' if (1) the patient's last SBT prior to extubation resulted in the generation of an EA report that was shown to the physician (if in intervention arm) and (2) the clinical outcome CRF is complete in either arm. In cases where the completion of the 'Clinical Outcome Information' CRF is not possible (eg, for the intervention arm, when extubation did not follow the generation of an EA report), the patient will remain enrolled, but results will not be included in final analyses, and those patients will be deemed incomplete.

Data management

The Dynamical Analysis Laboratory (DAL) at the Ottawa Hospital Research Institute will be responsible for monitoring and supporting EA software. Waveform data collected from vital sign monitors at the bedside (ie, capnography) and EA reports with direct identifiers removed will be transferred directly from participating sites to the DAL for the purpose of ensuring proper functioning of EA and for quality assurance. These data will be reported to the principal investigator (ie, Dr Karen Burns, Unity Health). Waveform data and EA reports with direct identifiers removed will be retained and used by the DAL for their own research and quality improvement purposes, including for EA quality improvement. These data will not influence the outcome of this study.

Statistical data analysis

Trial reporting will follow the CONSORT guideline.[70] All analyses will adhere to the intention-to-treat principle.

Primary outcome

We will report recruitment rates using proportions and means (SD) (alternatively medians (IQR) based on data distribution) overall and at participating centres.

Secondary outcomes

We will report rates of recruitment, consent, randomisation, protocol adherence, crossover and complete outcomes reporting using proportions. We will report physician perceptions of the usefulness of the EA tool (by centre, physician experience and physician sex) using frequencies and percentages, by participating centre and overall, together with 95% CIs.[71] We will assess time to successful extubation (from randomisation) to inform future sample size estimates.

We will proceed with the definitive RCT provided that recruitment, randomisation, protocol adherence, crossover and data collection are deemed feasible. If accrual and adherence targets are met, we will not make changes to the design of the future trial. We plan to roll the pilot trial patients forward into a large-scale trial if no significant changes are made to the intervention or trial protocol. If our accrual rate is marginal, we will review excluded patients and reasons for exclusion and reconsider the necessity for each criterion that accounts for a large number of excluded patients. If accrual rates are variable across sites, we will prioritise including sites who meet accrual targets for the future planned trial. Failure to achieve protocol adherence targets or high crossover

rates will require that we reconsider the study design and implementation (Online supplement 2).

Interim analyses

We will conduct an interim analysis at 50% (n=50) of recruitment for safety (extubation failure). We define extubation failure as requiring reintubation within 48 hours of extubation or disconnection from the ventilator for tracheostomised patients. The Data Safety and Monitoring Board (DSMB) meeting will include open (review of accrual, reasons for exclusion, withdrawals) and closed (review safety and patient-specific and treatment-specific data) sessions. A process is outlined in the DSMB charter to view unblinded data, at the Chair's request, for safety concerns.

Data monitoring

The LEADS Multi-centre Research Coordinator and Study Monitor will oversee enrolment rates and monitor patient-level data. The LEADS Steering Committee is comprised of a subgroup of co-investigators including the principal investigator, senior intensivists and trialists, biomedical engineers, site leads, and a patient and family advisor. The Methods Centre will provide support for data management and analysis. We have engaged a national intensivist, international intensivist, statistician and a separate patient and family advisor to serve on the DSMB. The DSMB will meet at 50% patient accrual to assess trial progress and safety. Either the international or the national intensivist will chair the DSMB. The DSMB meeting will include an open session to review trial progress in a blinded manner (accrual, reasons for exclusion, withdrawals) and a closed session to review safety, patient-specific and treatment-specific data. Only the DSMB members will be able to view unblinded data (at the Chair's request) if safety concerns arise.

Patient and public involvement

Two patient and family partners (AG, PK) were involved in protocol development.

Monitoring for harm

The LEADS pilot trial is low risk. We will use the best current recommendations regarding screening frequency and SBT conduct in both trial arms. The EA tool will inform rather than direct patient care during extubation. As such, we will record sentinel events in extubation decision-making (time to passing an SBT, deemed ready for extubation, first extubation, first successful extubation). Safety events (Box 2) will be recorded during the SBTs. All Adverse Device Effects will be assessed by the Site Investigator for severity, seriousness, expectedness and causality/relatedness (online supplement 2). The DSMB will monitor extubation failure rates (safety) at one planned interim analysis.

Ethics and dissemination

The LEADS Pilot Trial is approved by the Research Ethics Boards of all participating centres and Clinical Trials Ontario (4008). We will disseminate the LEADS trial findings through conference presentations and publication. Trial data will be made available, upon approved request, 1 year after article publication.

Box 2 : Adverse Event definitions

An Adverse Event (AE): any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the medical device, which includes:

a. events related to the medical device or the comparator; and
b. events related to the procedures involved.

In this device study, for users or other persons, the definition of AE is restricted to events related to medical devices and considered as Adverse Device Effects (ADE) or adverse events related to the SBT procedure.

Note 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device.

Note 2: This definition includes any event resulting from use error or from intentional misuse of the medical device.

A Serious Adverse Event (SAE) or Serious Adverse Device Effect (SADE) is any untoward medical occurrence or effect that :

a. led to death,
b. led to serious deterioration in the health of the subject, that either resulted in

1. a life-threatening illness or injury, or
2. a permanent impairment of a body structure or a body function, or
3. in-patient or prolonged hospitalisation*, or
4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c. led to fetal distress, fetal death or a congenital abnormality or birth defect.

*Planned hospitalisation for a pre-existing condition, or a procedure required by the Clinical Investigation Plan, without serious deterioration in health is not considered a serious adverse event.

DISCUSSION

Timely and safe liberation of critically ill patients from invasive ventilation is vitally important as prolonged mechanical ventilation and failed attempts at extubation, requiring reintubation, are associated with increased morbidity, mortality, costs, ICU LOS and risk for transmission of infection to healthcare providers through aerosolisation. Growing evidence supports strategies to liberate critically ill patients from ventilators; however, evidence to support extubation decision-making is lacking.

Preparatory work for this pilot trial included work conducted within two parallel research programmes investigating weaning and extubation conducted under the auspices of the Canadian Critical Care Trials Group. National and international weaning surveys identified daily screening and SBTs as current standards of care.[6 19] A national cohort study (n=680; 931 SBTs, 8 Canadian centres) identified significant intrainstitutional and interinstitutional variability in how SBTs were conducted and

reported to physicians.[34] An international observational study of mechanical ventilation discontinuation practices identified considerable practice variation in most aspects (screening, SBT conduct) of weaning.[72] Both conventional and network meta-analyses of alternative SBT techniques suggest that patients who underwent PS versus T-piece SBTs were 7–8% more likely to be successfully extubated,[73 74] although these findings have not been confirmed by an equivalence trial. By contrast, considerably less is known about extubation decision-making. A systematic review of 48 studies (n=10 946) found that the RSBI (< 105 breaths/L) had moderate sensitivity (0.83 (95% CI, 0.78 to 0.87)) but poor specificity (0.58 (95% CI, 0.49 to 0.66)) to predict extubation success with a diagnostic OR (DORs) of 5.91 (95% CI, 4.09 to 8.52).[33] The WAVE study identified that both reduced HRV and RRV during SBTs were associated with extubation failure and enabled derivation of novel predictive model (the WAVE score) to predict the probability of extubation failure.[47] A single-centre mixed-methods study demonstrated the feasibility of generating and delivering EA reports (<~15 min) and their acceptability to RTs and physicians.[75] A three-centre mixed-methods study clarified the ability to integrate the EA tool into bedside workflow and attained most metrics assessed (ability to consent participants (threshold 50%), capture complete data (threshold 90%), generate and review EA reports in real-time (thresholds 75% and 80%), respectively) and achieved all but one feasibility metric (EA report review).[76] Finally, an economic modelling analysis, we identified that even if the EA tool reduced extubation failure by at least 0.25%, hospitals could expect a positive return on investment.[17] Only two other studies have specifically examined extubation decision-making.[77 78] A survey of the diagnostic properties of extubation decision-making (n=45 intensivists) identified moderate sensitivity (57%), low specificity (31%), low accuracy (receiver operating characteristic area under the curve (ROC AUC) 0.35) and fair between-physician agreement (phi 0.37±0.15).[77] A single-centre, longitudinal study found that *protocolised* assessments of extubation readiness decreased extubation failure rates.[78] Despite the fact that weaning and extubation are routinely performed in ICUs, there is a paucity of evidence to guide clinical practice. There is a strong need to advance the science of extubation decision-making to better predict extubation outcome.

To enhance the feasibility of recruitment in the LEADS trial, we will use a hybrid consent model, recognising that it is 'practicable' in mechanical ventilation studies where recruitment is time sensitive and the interventions involve minimal participant risk.[79] This model prioritises obtaining consent from patients or surrogates whenever feasible but enables use of deferred consent for patients whose SDM is not available or may not exist with the expectation of obtaining consent from the patient or SDM after enrolment.

In designing this necessarily unblinded trial, we adopted several strategies to enhance internal validity and reduce bias. We aimed to limit *selection bias* by using central randomisation with full allocation concealment. To minimise identification bias, participants will be identified by lead RCs and RTs at participating centres. Although patients, clinicians and research personnel cannot be blinded to the assigned interventions, we will blind statisticians to treatment assignment. We aimed to select feasibility metrics that could be objectively measured, thereby decreasing bias related to outcomes adjudication. Although conventional extubation criteria will inform extubation in both arms, they will only be *protocolised* using a standardised written checklist in the EA arm. During trial implementation, we will monitor protocol adherence in both arms. We recognise that contamination of the standard care arm by use of the EA tool is unlikely but may occur. Consequently, we planned to measure bidirectional crossovers in the LEADS trial reflecting the percentage of SBTs wherein an EA report was (standard care arm to EA arm) or was not (EA arm to standard care arm) generated, delivered or reviewed by physicians. We will limit performance bias by seeking buy-in through extensive education and training of personnel at participating centres prior to pilot trial activation. Whereas site RCs and RTs will be trained to harvest and record capnography waveform data during SBTs, complete extubation checklists, transmit data and interpret EA reports, physician site leads will be extensively trained on the trial protocol to provide trial oversight at their centres. Several potential cointerventions may be used by clinicians in the postextubation period including high-flow nasal cannula and non-invasive ventilation (NIV). We will record the use of these strategies in both trial arms during the pilot trial. Variable use of these postextubation support strategies may suggest the need for protocolisation in a larger trial.

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