Extubation Advisor: initial implementation and evaluation of a novel extubation clinical decision support tool

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Site Investigator Signature Page

Protocol Title: Extubation Advisor: initial implementation and evaluation of a novel extubation clinical decision support tool

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I have read and understand the protocol, and I agree that it contains all the ethical, legal and scientific information necessary to conduct this study. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I will work according to the principles of Good Clinical Practice (GCP), Canadian Tri-Council Policy Statement version 2 (TCPS2), the Declaration of Helsinki (2004), Part 3 of the *Medical Devices Regulations*, and applicable health information protection regulations and privacy policies. Further, I will conduct the study in keeping with local and regulatory requirements. I will provide copies of the protocol and access to all relevant information to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study.

_____ _____

Site Investigator's Signature Date

1. Brief Summary

Expeditious, safe extubation is vitally important in the care of Intensive Care Unit (ICU) patients, as prolonged mechanical ventilation harms patients and failed extubation (i.e. re-intubation within 48 hrs) is associated with increased morbidity, mortality and costs. The urgent need to improve extubation failure is further highlighted by current observations suggesting that COVID-19 patients are at increased risk of both early and late extubation failure. We previously found that decreased respiratory rate variability (indicative of reduced adaptability and/or increased stress) during Spontaneous Breathing Trials (SBTs) predicted extubation failure and outperformed the best available predictive indices. Combining this predictive analytic with standardized extubation readiness checklists and risk mitigation strategies, we created the **Extubation Advisor**™ (EA). We recently completed a single-center phase I mixed methods observational study (n=117) wherein we demonstrated technical feasibility (i.e. ability to generate 92% of EA reports) and clinician acceptance of the EA tool. In the current open-label, multi-center interventional phase I study, we will assess the feasibility and initial perceptions of EA implementation in the intensive care unit by (1) evaluating the feasibility of patient enrolment, data collection, and EA report generation, and (2) performing a mixed-methods analysis of critical care physician and respiratory therapist perceptions of EA. Findings from this study will inform a future randomized controlled trial assessing EA outcomes compared to standard of care, with the intent of aiding bedside decision-making, enhancing care delivery, and improving outcomes in critically ill patients with and without COVID-19.

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2. Background

2.1. Background and rationale for clinical implementation of Extubation Advisor

Expeditious and safe extubation (endotracheal tube removal) in critically ill patients is a vitally important transition from life support to spontaneous breathing. Prolonged invasive ventilation and failed extubation (i.e. re-intubation <48 hrs; 15% incidence) are associated with increased morbidity, mortality, cost, and increased risk to health care personnel due to aerosolization[1–6].

Intensive Care Units (ICUs) globally now face the additional challenge of treating COVID-19 patients, with record numbers of patients requiring ventilator support. Current data support that 60-75% of COVID-19 patients admitted to the ICU present with acute respiratory distress syndrome (ARDS) and respiratory failure requiring intubation and invasive ventilation[7]. Although no published data have characterized the epidemiology (incidence, causes, consequences) of extubation failure, ICU clinicians worldwide have identified on various social media platforms that critically ill patients afflicted with COVID-19 have an increased incidence of extubation failure.

For critically ill patients, a spontaneous breathing trial (SBT) is the current standard of care to assess 'extubation readiness'. SBTs are focused assessments of a patient's ability to tolerate minimal ventilatory support over 30-120 minutes and are performed by respiratory therapists (RTs) working collaboratively with ICU physicians to oversee ventilator management in the ICU. A rapid shallow breathing pattern during an SBT is worrisome and portends failure. Nevertheless, even the most widely used measurement, the respiratory frequency to tidal volume ratio also known as the rapid shallow breathing index (RSBI), has limited value in predicting whether patients will be successfully extubated[8–10].

Recognizing the implications of a failed attempt at extubation to patients and healthcare systems, significant interest has emerged in identifying strategies that aid bedside clinicians to better predict extubation success and failure[11–16]. ICU clinicians typically monitor critically ill patients using waveforms (e.g. electrocardiography, capnography, oxygen saturation, etc.). Although waveform data is sampled hundreds of times per second, vital signs are commonly charted per hour, thus ignoring valuable information regarding the complexity or variability of the heart or breathing rate. Decreased heart rate variability (HRV) and respiratory rate variability (RRV) are associated with illness, age, and stress, indicating reduced adaptability and physiologic reserve. Variability analysis documents degree and character of fluctuations of these physiologic parameters over intervals-in-time. Several small studies have demonstrated that reduced HRV or RRV during SBTs is associated with extubation failure[17–23].

In 2014, we completed and published the large, prospective, observational, multicenter Weaning and Variability Evaluation (WAVE) study (n=721) addressing the ability of HRV and RRV to predict extubation outcomes in a heterogenous cohort of invasively ventilated critically ill patients[24]. We found that both reduced HRV and RRV during SBTs were associated with extubation failure ($p<0.007$) and derived a predictive model, known as the WAVE score, based on an average ensemble of logistic regression models including 5 measures of RRV. More importantly, the WAVE score demonstrated high and complementary predictive accuracy compared to conventionally used measures.

We subsequently created the *Extubation Advisor*^{TM} (EA) as an extubation decision support tool incorporating the WAVE score to aid bedside clinicians with extubation assessments. The one-page EA report combines (i) enhanced predictive ability of extubation outcomes based on RRV, (ii) standardized SBT reporting with extubation readiness checklists, and (iii) individualized extubation failure risk mitigation strategies. From a functional perspective, there are two unique users of the EA tool. During a patient's SBT, an RT connects the patient's bedside monitor to a computer containing the EA software and enters clinical and demographic patient information through the EA user interface. An EA report is generated following the SBT and evaluated by the ICU MD to help inform their extubation decision. Thus, the EA tool provides a means for ICU MDs to objectively evaluate and communicate assessments of individual patient's readiness for extubation and an estimate of each patient's risk for extubation failure.

In 2019, we conducted a single centre, phase I mixed-methods observational study to evaluate our ability to generate EA reports and clinical impressions of EA, involving 117 critically ill patients with 151 SBTs and 80 extubations (currently under peer review). We demonstrated that 92% of EA reports could be generated and found an incidence of extubation failure of 11% in low-risk patients, 21% in high-risk patients, and 38% when both the RRV-derived model and clinical impression were high-risk. We assessed clinical impression of the EA tool using questionnaires and qualitative interviews with RTs and MDs involved in using the EA tool and making extubation decisions, finding that clinicians involved in using EA perceived that it had good potential to aid in extubation decision-making.

EA is a software tool that will directly influence clinician decision-making, with short-term consequences for the patient; thus, as per Health Canada requirements, EA must be regulated as a medical device. In addition, to implement EA in a broad sense, it must be integrated into bedside monitors or ventilators, with reports available to the electronic heath record. Therefore, commercialization and regulatory approval are both required for clinical adoption. To accomplish this, Therapeutic Monitoring Systems (TMS), was founded by one of the co-PIs of this study, Dr. Andrew Seely, in order to help bring EA (and similar) products to the bedside. All TMS products are based on the combination of variability analysis and machine learning to create variability-derived predictive analytics. EA has been submitted in August 2020 for approval by Health Canada in the Interim Order (IO) program. In addition, submission to the FDA is planned for March 2021.

A large evidence gap exists regarding the epidemiology of extubation failure in critically ill adults that poses several clinical dilemmas for ICU clinicians involved in liberating patients from ventilators, particularly if they are afflicted by COVID-19. The proposed study will evaluate the feasibility and initial perceptions of EA implementation in the intensive care unit by evaluating the feasibility of patient enrolment and consent, data collection, and EA report generation and delivery, with the aim to aid bedside decision-making, enhance care delivery, improve patient outcomes, and inform the design of a future randomized controlled trial.

This study is part of the Ontario Bioscience Innovation Organization (OBIO) Early Adopter Health Network (EAHN). The aim of this network is to bridge the gap between research and procurement of novel technologies. Thus, following completion of the 3 month protocol, the underlying aim of the protocol is for clinicians and administrators at the participating centers to determine if they would **(1)** like to be an early adopter of EA (i.e. license the product at the conclusion of the study based on highly

favourable experience), or **(2)** would like to continue participating in research regarding EA (i.e. participate in a planned future pilot then definitive randomized controlled trial), or **(3)** do not wish to continue with any further evaluation of the EA tool (e.g. if for example, the tool does not function with the existing care pathways in their ICU).

2.2. Background and rational for mixed-methods analysis

Incorporating the Extubation Advisor tool meaningfully into practice will amount to implementation of a complex intervention, as defined by standard guidance on the topic[25]. Implementation of such interventions in the past has typically not been clearly described, designed systematically, or informed by theory of behaviour change[26], which has likely contributed to the relatively small likelihood of success of these interventions[27]. We will engage in a systematic, theory-informed development process informed by two complementary frameworks[28]: French's approach for theory-informed intervention development[29], and User Centered Design[30].

The French framework for intervention development describes a stepped approach based on 4 guiding questions: 1) Who needs to do what differently? 2) Using a theoretical framework, which barriers and enablers need to be addressed? 3) Which behaviour change techniques and modes of delivery are best suited to overcome barriers? 4) How can the behaviour(s) be measured and understood? User-Centred Design (UCD) describes an iterative process of design, evaluation, analysis, and re-design intended to result in a final product that meets pre-determined usability goals (e.g. 90% of the time, physicians should be able to read, understand, and make an extubation decision based on the EA report in less than 5 minutes). UCD has been shown in a variety of contexts to improve user satisfaction[31], reduce errors in navigation and the resulting confusion[30,32], and to increase the efficiency with which the information can be found, understood, and used[33]. Together, these frameworks can be employed to identify and rectify barriers and drivers to use of EA, as well as ensuring that the tool itself is optimally clear and useful for extubation decision-making.

3. Conflict of Interest

Therapeutic Monitoring Systems (TMS) is the commercial partner of the Dynamical Analysis Laboratory (DAL) within the Ottawa Hospital Research Institute, as TMS owns the rights to the intellectual property developed by the DAL. Several issued and pending patents form the DAL IP portfolio, including a patent underlying the technology of Extubation Advisor (US Patent 9,785,745 B2; issued Oct 10, 2017). Dr. Andrew Seely is one of the inventors of the patent, is Founder and CEO of TMS, and is Director of the DAL. In addition, Dr. Christophe Herry is one of the inventors related to the EA patent. The EA patent is owned by the OHRI, and TMS and OHRI have a partnership agreement as well as IP option agreement in place. TMS, DAL and the OHRI share the same objective, namely the development and commercialization of novel variability-derived clinical decision support tools in order to improve care.

To manage this conflict of interest (CoI), the following are in place: (1) Dr. Seely discloses the CoI in all grants, publications, presentations, and other public communication, and submits a CoI management agreement to the OHRI annually. (2) Dr. Seely will not be involved in recruitment of his own patients for this study. (3) All analyses performed by Christophe Herry and/or Andrew Seely within the DAL will be blinded to extubation outcomes. (4) Dr. Brehaut will supervise the analysis and interpretation of the

qualitative (i.e. interviews) results, and (5) Dr. Burns, co-PI and co-chair the Steering Committee, will supervise the analysis and interpretation of the quantitative (i.e. analyses of feasibility) results of the study. In summary, transparency, public disclosure, scientific rigour, patient-centered focus, and independent oversight have been and continue to be the foundations for this CoI management.

4. Research Question

What is the feasibility and the initial perceptions of a novel extubation decision support tool, Extubation Advisor, in the intensive care unit (ICU) in multiple centers?

5. Objectives

The primary research objectives of this study are to:

1. Evaluate the feasibility of:
    a. Patient enrolment and consent
    b. Wave form data capture
    c. Participant clinical data entry
    d. Extubation Advisor report generation and delivery to physicians
2. Perform a mixed-methods analysis of physicians and respiratory therapists regarding usability, perceived value, identified behaviours, perceived barriers and drivers, and perceived impact.

The secondary research objective of this study is to:

1. Evaluate the feasibility of completing the clinical case report form (CRF).

6. Study Outcomes

Primary objectives:

1. Implementation of Extubation Advisor will be considered feasible if:
    a. >50% of identified eligible patients are enrolled and consented,
    b. >75% of the time, wave form data is captured,
    c. >90% of the time, participant clinical data is fully entered into the EA tool,
    d. >80% of the time, an extubation report is successfully generated and delivered to the attending physician.
2. Usability, perceived value, identified behaviours, perceived barriers and drivers, and perceived impact will be assessed through interviews with RTs and MDs.

Secondary objectives:

1. Completion of the clinical CRFs will be considered feasible if >90% of clinical CRFs are complete.

7. Design

This is an open-label, multi-center interventional Phase 1 study to implement and evaluate perceptions of Extubation Advisor in consenting patients in the intensive care unit.

8. Centers

This study will be conducted at two Ontario academic hospitals: The Ottawa Hospital and Unity Health Toronto.

9. Sample Size and Timeline

9.1. Sample size for clinical implementation of Extubation Advisor

We will enroll a total of 72 patients, including patients both with and without COVID-19, able to provide informed consent, through a surrogate. We anticipate that 1 patient will be enrolled per week at each ICU (average of 24 patients per month), with enrolment occurring over a period of 3 months, and that there will be a 20% loss due to protocol deviation, loss of data, inability to provide a complete extubation CRF, etc. This will leave 58 patients with complete CRFs, which we anticipate 9-10 will experience extubation failure.

This will allow a robust evaluation of feasibility outcomes, including consent rates, waveform and clinical data collection, and report generation – see section 5 above). Over several months, individual clinicians will likely be in the ICU 3-5 weeks, and be exposed to 5-10 patients with EA, which we feel is adequate to provide their initial perceptions of usability.

9.2. Sample size for mixed-methods analysis.

We will interview up to 10-15 physicians and 10-15 respiratory therapists, distributed equally among participating sites, up to a maximum of 2 times. Repeated interviews will be conducted only when the study team deems the tool to have changed enough to warrant being seen again by the same people. Enrolment of 10-15 physicians and 10-15 respiratory therapists will be sufficient for thematic data saturation based on previous evidence supporting sizes of 10 to 13 participants in both theory-based and non-theory-based qualitative interviews[34,35].

10. Eligibility

10.1. Inclusion and Exclusion Criteria for Patient Participants

Inclusion Criteria

Adult patients (≥18 years of age) with or without COVID-19 in the intensive care unit (ICU) able to provide informed consent (through a surrogate) and who meet the following criteria:

- Current invasive mechanical ventilation and anticipated to remain on invasive mechanical ventilation for at least 48 hours
- Ready for spontaneous breathing test (SBT) for assessment for extubation
- At least partial reversal of the condition precipitating mechanical ventilation
- Stabilization of other organ systems

- Toleration of pressure support ventilation ≤14 cm H_2O, (oxygen saturation (SpO_2) ≥90% with fraction of inspired oxygen (FiO_2) ≤40% and positive end-expiry pressure (PEEP) ≤10cm H_2O)
- Hemodynamic stability (low – phenylephrine <50 ug/min; norepinephrine <5 ug/min; dobutamine <5 ug/kg/min; milrinone <0.4 ug/kg/min – or no vasopressors)
- Stable neurological status (no deterioration in Glasgow coma score during prior 24 hours and, if measured, intracranial pressure (ICP) <20 mmHg)
- Intact airway reflexes (adequate cough with suctioning and a gag reflex)

Exclusion Criteria

- Order not to re-intubate should the patient fail extubation
- Anticipated withdrawal of life support
- Known or suspected severe weakness (myopathy, neuropathy, or quadriplegia)
- Tracheostomy
- Prior extubation during current ICU stay

10.2. Inclusion and Exclusion Criteria for Extubation Advisor Users

10.2.1 Inclusion and Exclusion Criteria for RT Users

Inclusion Criteria

Respiratory therapists who consent to participate in an interview and are the enrolled patient's:

- Respiratory therapist who has input data into the Extubation Advisor tool

Exclusion Criteria

- Respiratory therapist is unable to complete the interview in English

10.2.2 Inclusion and Exclusion Criteria for MD Users

Inclusion Criteria

Physicians who consent to participate in an interview and are the enrolled patient's:

- Attending ICU physician and/or fellow

Exclusion Criteria

- Attending ICU physician or fellow is unable to complete the interview in English

10.3. Co-enrolment

Given that this study is a feasibility and usability assessment, participant co-enrolment with other studies whose outcomes are unrelated to weaning and extubation will be permitted. We propose to allow co-enrolment with the Frequency of Screening and Spontaneous Breathing Trial Technique (FAST) RCT led by co-PI Dr. Karen Burns even though it is directly related to weaning and extubation, for several reasons: the proportion of patients expected to be co-enrolled with be exceptionally small, the frequency

of SBT screening will not affect the EA assessment, and both arms of the SBT technique (no vent support vs minimal 5/5 PS/PEEP settings) are acceptable for an EA assessment as they represent variable institutional practice and were included in the original WAVE study. Thus, we have no limitations on co-enrolment.

11. Study Procedure

11.1. Study procedure for clinical implementation of Extubation Advisor (EA)

Eligible patients will be identified by RTs or Research Coordinators (RCs) in the ICU for SBT and assessment of extubation. A surrogate will be identified and contacted to provide informed consent on behalf of the eligible patient, after which the eligible patient will be enrolled. No formal screening log will be completed, and RTs/RCs will attempt to identify as many eligible patients as is feasible.

When an eligible patient is identified and enrolled, they will be connected to a bedside or portable monitor displaying ECG and capnography (and other waveforms). Capnography requires a CO_2 module in the monitor, connected to the endotracheal tube by capnography sampling tubing. The RC will first confirm that the patient monitor to be used is compatible with the EA software. An EA laptop will be connected to the monitor through a serial cable. The waveform and vital sign data will undergo processing directly on the laptop using the EA software.

An RT will prepare the patient for an SBT, making sure that the Capnograph (CO_2) module is installed on the monitor, that the CO_2 sensor is on the tubing prior to starting the SBT, and that a CO_2 signal is seen at the monitor. The RT will log on to the EA application and input the patient's demographic and admission information (one-time data entry performed in less than 2 min). The RT will then get feedback from the EA application that it is receiving the vital signs waveform data and that it includes a capnograph (CO_2) waveform (i.e. two separate but related requirements) and displays that the system is ready to go.

With the system indicating it is ready to go, the RT will press the "Start" recording button, initiating the waveform recording. They can then enter the starting (i.e. pre-SBT) ventilator (i.e. PS/PEEP values) and sedation score (i.e. RASS score) into the EA system (~20 sec). The RT will start the SBT by lowering PS/PEEP settings on the ventilator to whatever is ordered by the clinician and clicking the "Start SBT" button in EA to initiate the recording. While the waveforms are being recorded, the RT will complete the rest of the admission information, comorbidities, and extubation readiness checklist (<5 min). At the end of the SBT, the RT will stop the recording (or cancel the SBT if <15 minutes).

The EA system will process the portions of CO_2 waveforms and vital signs data corresponding to the SBT and proceed to clean and assess the quality of the data, compute variability metrics, and generate a score summarizing the risk of extubation failure.

The RT will then put the PS/PEEP back to normal on the ventilator and complete the SBT Outcome Information and their own impression of the risk of extubation failure (<2 min). The RT will click on the "Generate Report" button, which displays a PDF report on screen. The RT will then review the report with the attending physician and determine whether to proceed with the extubation or not. If desired, the EA report may be emailed to a secure hospital email with the actual report attached for printing, so that

the RT may physically give the report to the attending MD, or place it at the bedside. This process may be repeated every time an SBT is repeated for assessment of a patient's readiness for extubation, until the patient undergoes planned extubation, or reaches an alternate outcome (self-extubation, direct to tracheostomy, death, transfer to another institution). RTs who complete EA data entry during the SBT will receive a $10 coffee gift card, limited to a maximum of 3 gift cards per patient for repeated SBTs, as a token of appreciation for their time and expertise.

After a minimum of 72 hours after extubation, the site Research Coordinator will complete a short **Clinical Outcome CRF**, which will include the time of extubation, the outcome of extubation, the need and timing of re-intubation (if present), the need for non-invasive ventilation or high flow heated humidity, all within the 72 hours post-extubation. Last, the Clinical Outcome CRF will include the date of ICU discharge and the status of the patient at that time. Patients who remain hospitalized at 72 hours will be followed via their electronic medical record until hospital discharge.

11.2. Definition of complete CRF

A patient and their 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, and **(2)** the clinical outcome CRF is complete. In cases where the completion of the "Clinical Outcome Information" CRF is not possible (e.g. when extubation did not follow the generation of an EA report, if a tracheostomy was performed, etc.) the patient will remain enrolled, but results will not be included in final analyses, and those patients will be deemed incomplete. Funding will thus prioritize complete patient data collection. Additional funding will be provided if multiple SBTs are captured in the same patient.

11.3. Study procedure for mixed-methods analysis

As the first phase in design and implementation of this complex intervention, we will conduct a series of short interviews with consenting respiratory therapists (RTs) involved in using the EA tool and critical care physicians (MDs) involved in extubation decisions for ventilated patients in the ICU, based on their experience of using EA and conducted within 96 hours of their actual patient extubation decisions.

In a general sense, these interviews will be designed to address Question #1 of the French Framework ('Who needs to do what differently?'), obtain initial opinions about Question #2 ('What barriers and enablers need to be addressed?'), and identify initial usability issues. Subsequent phases (the subject of a separate proposal) will involve more detailed evaluation of barriers to and drivers of EA usage using the Theoretical Domains Framework (Question #2)[36,37], assessment of optimal behaviour change techniques and modes of delivery (Question #3), and more formal UCD testing, both conducted in the context of a more formalized version of the tool.

All RTs and MDs will be informed that their participation in the study means they may be contacted by email to ask if they would be interested in participating in an interview. Potential interviewees (i.e. RTs/MDs who used the Extubation Advisor software and/or report) will then have their name and email address provided to the lead site to be contacted by the study team, consented, and asked to participate in a 15 to 30-minute interview within 96 hours of the patient extubation decision. The RT or MD may also provide their phone number to the lead site if they do not wish to conduct the interview via

videoconference. Interviews with MDs will include an evaluation of the report only and are expected to take approx. 15 min. Interview with RTs will include an evaluation of both the report and data entry and are expected to take approx. 30 min. EA reports will be shared with the participating RT or MD at the time of the interview through email, screen-sharing, or web-link. Interviewees will review the consent form and provide their verbal consent to participate at the start of the interview. The interview guide is described in the **"Extubation Advisor Interview Guide for RTs and MDs"** document. Interviews will be divided into 4 sections. After instructions are provided, Section 1 includes an icebreaker in which the interviewee is asked whether they remember the patient whose details are being provided in the report, and whether they remember what their extubation decision was for that patient. Additional patient details will be provided by the interviewer as needed to orient the interviewee. Section 2 will involve a 'think aloud' instruction, in which the interviewee is asked to review the EA report while verbalizing any thoughts they have, as well as reading the material out loud. This approach is effective at identifying issues of misinterpretation and confusion of complex information[38,39]. Section 3 will ask a series of questions about the EA report itself, including 1) What they think about it overall? 2) Would they use it in their practice? 3) Can they identify any clear barriers to them using it in their practice? 4) Can they identify any issues that would make them more likely to use it in their practice? and 5) What improvements would they suggest? For RTs with experience in entering the data to prepare the EA report, Section 4 will ask them to reflect on the data entry process to propose improvements and identify barriers and drivers to successful data entry. Interviews will be audiotaped, and filed notes taken during the interview. All RTs and MDs who participate in an interview will receive a $75 gift card (participant choice between Amazon, Chapters, or Tim Hortons) as a token of appreciation for their time and expertise.

12. Evaluation

12.1. Feasibility evaluation of Extubation Advisor

To evaluate the feasibility of Extubation Advisor implementation we will quantify:

1. The number of identified eligible patients enrolled and consented to capture the proportion of both (a) patients enrolled and (b) patients not enrolled due to patient/caregiver refusal.
2. The proportion of useable recordings and data fully entered, and report on the reasons for failure.
3. The number of reports successfully generated and transmitted to physicians, and report on the reasons for failure.

To evaluate the feasibility of completing clinical CRFs we will quantify the number of clinical CRFs that have been deemed complete.

12.2. Mixed-methods evaluation

Audiotapes will be transcribed for later coding by two coders. Based on field notes (and referring to audiotapes as necessary), issues of usability and clarity will be assembled and reviewed by the study team every 2-4 interviews, and modifications made for subsequent interviews. Issues that cannot be dealt with by simple modification of the EA report will be later analyzed with barriers/drivers analysis according to the Theoretical Domains Framework[36,37], which organizes over 100 constructs known to be associated

with behaviour change into 14 domains that can categorize barriers to and drivers of professional health behaviours. The approach has also evolved to include systematic methodologies for identifying what specific interventions will overcome these barriers[29,40,41]. Our team has considerable experience with this framework.

13. Safety Reporting

13.1. 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 investigational medical device, which includes:

- events related to the investigational medical device or the comparator; and
- 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 investigational medical devices, and considered as Adverse Device Effect (ADE).

Adverse Device Effect (ADE): Adverse Event related to the use of an investigational device. Note 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational device. Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational 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 hospitalization*, 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 hospitalization 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.

13.2. Recording

All Adverse Device Effects (ADE) need to be assessed by the Site Investigator for severity, seriousness, expectedness, and causality/relatedness. See descriptions below:

• Severity (intensity): Events/reactions are usually classified as mild, moderate or severe. General definitions for severity categories are often provided in the protocol, and specific definitions for particular types of events, e.g., for mild, moderate, or severe hepatitis, may also be provided depending on the study. The terms serious and severe are not synonymous.

• Seriousness: Events/reactions are classified as serious if associated with effects threatening the life or physiological functions of a subject. Seriousness criteria include death, hospitalization (initial or prolonged), persistent or significant disability, life threatening, congenital anomaly, or medically relevant adverse reaction. The seriousness of a reaction determines if it should be reported to the Manufacturer or Regulatory Correspondent and regulatory authorities.
• Expectedness: Events/reactions are classified as unforeseen or unexpected if, by nature or intensity, are not reported in the Investigator Brochure or Device User Manual.

• Causality/Relatedness: Events/reactions are assessed, according to the investigator's clinical judgement, if there is a reasonable doubt as to causal relationship. Attribution may be related, possibly related, probably not related, or unknown.

13.3. Safety Reporting Responsibilities of Site Qualified Investigator

The qualified investigator is required to report serious adverse events or Serious Adverse Device Effect (SADE) to Health Canada AND to the Regulatory Correspondent **within 72 hours of discovery**. This includes cases in which the incident:

a) is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labelling or in its directions for use, or
b) has led to the death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur, whereas
    i. A serious deterioration in health means a life-threatening disease, disorder or abnormal physical state, the permanent impairment of a body function or permanent damage to a body structure, or a condition that necessitates an unexpected medical or surgical intervention to prevent such a disease, disorder or abnormal physical state or permanent impairment or damage.
    ii. The term "permanent" means irreversible impairment or damage to a body structure or function, and necessarily excludes minor impairment or damage.
    iii. Medical intervention is not in itself a serious deterioration in health. The reason that motivated the medical intervention should be used to assess the reportability of an incident.

It is expected that any serious untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device, will be reported.

Health Canada does not currently have a mandatory form specifically for healthcare professionals. In the interim, healthcare professionals can submit their ITA incidents using the *Mandatory Medical Device Problem Reporting Form for Industry*. The report should clearly state that the device was approved under Part 3 of the *Medical Devices Regulations*.

How Can the Site Qualified Investigator Submit the Report to Health Canada:
Completed forms should be emailed to: hc.mdpr-dimm.sc@canada.ca or faxed to: 613-954-0941 or mailed to:

Canada Vigilance - Medical Device Problem Reporting Program
Marketed Health Products Directorate
Health Canada
Address Locator 1908C

200 Tunney's Pasture Driveway
Ottawa (Ontario) K1A 0K9

Any non-serious or serious device effect will be reported to the local governing Research Ethics Board if meeting the REB's reporting requirements.

13.4. Safety Reporting Responsibilities of the Manufacturer/Importer

For an incident that occurs in Canada, the manufacturer/importer is required to provide a preliminary and a final report in respect of the incident. The safety reporting responsibility of the Manufacturer/Importer has been delegated to the Regulatory Correspondent. The preliminary report shall be submitted:

i. Within 10 days after the manufacturer/importer of a medical device becomes aware of an incident, if the incident has led to the death or a serious deterioration in the state of health of a patient, user or other person, or
ii. within 30 days after the manufacturer/importer of a medical device becomes aware of an incident, if the incident has not led to the death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur.

Not all incidents lead to a death or to a serious deterioration in health, either owing to circumstances or to the timely intervention of health care personnel, for example. These situations are known as near incidents. If the incident, in the case of recurrence, could lead to a death or to a serious deterioration in health, a report to Health Canada must be submitted within 30 calendar days.

This requirement also applies if the examination of the device, or a deficiency noted in the information supplied with the device, or any information associated with the device, indicates some factor which could lead to an incident involving death or serious deterioration in health.

The incident report can be submitted according to the procedure outlined for the *Mandatory Medical Device Problem Reporting Form for Industry*. The report should clearly state that the device was approved under Part 3 of the *Medical Devices Regulations*.

The authorization holder should submit a report of the incident to Health Canada even if the clinical trial was terminated prematurely.

How Can the Regulatory Correspondent Submit the Report to Health Canada:
Completed forms should be emailed to: hc.mdpr-dimm.sc@canada.ca or faxed to: 613-954-0941 or mailed to:

Canada Vigilance - Medical Device Problem Reporting Program
Marketed Health Products Directorate
Health Canada
Address Locator 1908C
200 Tunney's Pasture Driveway
Ottawa (Ontario) K1A 0K9

Submission of a report does not constitute an admission that medical personnel or the health product caused or contributed to the incident.

For further information on the Mandatory Medical Device Problem Reporting by Industry, please refer to: *Guidance Document for Mandatory Problem Reporting for Medical Devices*.

14. Data Management

In order to predict the risk of extubation failure, the EA tool will be hosted on a Windows-based tablet or laptop with data acquisition software pre-installed and configured for the collection of vital sign waveform data from bedside monitors via a serial connection. Demographic and clinical data from patients enrolled in the study will be collected by respiratory therapists using the EA tool data entry interface in the intensive care unit.

Upon completion of data collection, automated algorithms will assess the quality of the waveform data, detect breaths, and perform cleaning of artifacts, missing data and noise, to form vital signs time series, which will be used to calculate variability metrics for the patient.

The resulting respiratory rate variability data will be fed into the trained EA predictive model, yielding a probability of extubation failure. A standardized checklist of clinical factors relevant to assess extubation readiness will be completed by the respiratory therapist via the EA user interface.

The EA report will be generated within minutes and will be made available to critical care physicians to assist with extubation decision-making. The report will contain a risk estimate of extubation failure, a standardized extubation readiness checklist, vital signs, the best professional impression of extubation readiness by the respiratory therapist, and possible mitigation factors to consider prior to extubating a patient. Only the treating physician and respiratory therapist performing the SBT will have access to the Extubation Advisor (EA) report, containing Personal Health Information (PHI) and Personal Identifying Information (PII), unless the treating physician or respiratory therapist participants in an interview to evaluate EA. In these cases, the researcher from the lead site will be able to view the patient's PHI/PII on the EA report during the interview (name, date of birth, medical device identifier, MRN) but this information will not be stored by the lead site. Reports containing PHI and PII will temporarily be stored encrypted on a hospital approved laptop running the EA app. This data will be combined with waveform data captured during the SBT and patient outcome data collected via the Case Report Form to create the local study database, stored within the local hospital firewall on a secure, credentials-controlled server. The laptop will be password protected and the EA app will also require a username/password to access. The local study database will have identifying PII/PHI removed (name, date of birth, medical device identifier, and MRN) and replaced by unique patient and site identifiers using an automated script. Non-identifying PHI required to generate the EA report including age, sex and/or gender, admission date, discharge date, and date of death (if applicable) will remain in the study database. The link between the study IDs and identifying information will be maintained on the secure hospital server in a password protected excel file. Only the research personnel involved in this project will have access to this password protected file. The study database will be transferred to the lead site via secure upload, where all local study databases will be combined to create the final database for analysis.

The Dynamical Analysis Laboratory (DAL) at the Ottawa Hospital Research Institute will be responsible for monitoring and supporting EA software.

15. Study Management

A steering committee comprised of all investigators will meet monthly to discuss study progress, conduct, patient safety, and any issues that arise.

A Data Safety and Monitoring Board (DSMB) will not be established for this study but will be formed for a future definitive RCT with a far greater number of participants and both interventional and control groups following the successful completion of this feasibility study.

16. Study Administration

16.1. Ethical Conduct of the Study

The trial may only be initiated after the Participating Site has obtained written approval of the protocol, consent documents and/or other REB-required study documents, and any amendments (if applicable), by the governing Research Ethics Board (REB). Changes in protocol (amendments) must be submitted to the governing REB for approval.

For this Class III device, the Manufacturer or the Regulatory Contact are required to provide evidence of written approval from each REB along with study documents referenced in the REB approval to Health Canada prior to study initiation. This approval letter must reference the most current study documents (e.g. protocol and informed consent forms). REB approval should ideally be submitted with the ITA application. However, Health Canada will issue a "Letter of Authorization" for investigational testing, if the application meets the requirements stated in Part 3 of the Regulations and REB approval is not available at the time the ITA application review has been completed.

Prior to study initiation, written REB approval which references the most current study documents must be submitted by the Manufacturer or the Regulatory Contact along with a completed "Application for Revised Investigational Testing Authorization" to hc.devicelicensing-homologationinstruments.sc@canada.ca.

If REB approval references updated study documents, the Manufacturer or the Regulatory Contact must submit the following prior to study initiation:

1. a completed form titled "Application for Revised Investigational Testing Authorization"; and
2. updated red-lined and clean copies of the protocol and ICF document versions referenced in the REB approval. Please note that red-lined versions must show all changes made from the Health Canada approved version. If the protocol or ICF versions referenced in the REB do not differ from those indicated in the Letter of Authorization, the REB may be submitted to Health Canada without completing an application form. The information on the REB approval will be verified, and an acknowledgement of receipt will be sent.

16.2. Participant Information and Consent

Authorized research staff will explain to each potential Participant the aims, methods, reasonably anticipated benefits and potential hazards of the trial and any discomfort in an REB-approved format.

After this explanation and prior to performance of any trial related activity, Participants will give their informed consent in an REB-approved format.

16.3. Monitoring and Audit

In accordance with Part 3 the *Medical Device Regulations*, and/or relevant ICH guidelines, the Sponsor or a designee will periodically inspect all completed study case report forms (see Section 10.4), study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times during and after completion of the study. The aforementioned responsibilities will be assumed by the regulatory correspondent, Dr. Seely at OHRI, or a designee.

As specified in the Study Monitoring Plan, the monitoring visits provide the Sponsor or the Regulatory Correspondent with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of data in the completed case report forms; ensure that all protocol requirements, applicable Health Canada and other relevant regulations, and investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) for the subjects in this trial. The names and identities of all research subjects will be kept in strict confidence and will not appear on electronic data entry forms or other records provided to or retained by the Sponsor or the Regulatory Correspondent. The investigator/institution guarantees direct access to source documents by the Sponsor and appropriate regulatory authorities.

The trial site may also be subject to review by the REB, to quality assurance audits performed by the Sponsor or the Regulatory Correspondent, and/or to inspection by Health Canada.

17. Investigational Testing Report

After closure of the investigational testing, the manufacturer or importer should submit a report of the study to Health Canada even if the investigation was terminated prematurely. This responsibility has been delegated to the Regulatory Correspondent.

a. The report should include identification of the device, a description of the methodology and design of the investigation, any deviations from the protocol, data analysis together with any statistics and a critical appraisal of the aims of the investigation.
b. The report should take into account the data from each investigation site and for all subjects. No subjects should be identifiable either from the investigation report or the published results.
c. Where applicable, the investigation testing report should be made available to the principal investigator and all investigators for review and comment. The sponsor and the Regulatory Correspondent shall maintain records confirming that the report has been provided for review. If a reviewer does not agree with all or part of the report, their comments should be recorded and communicated to the other principal investigators.
d. The sponsor and coordinating investigator should provide their signatures, indicating their agreement with the content of the report. If no coordinating investigator is appointed, the signature of the principal investigators should be obtained.
e. The report should be provided to the REB.

18. Record Retention

To comply with Health Canada regulations, the trial related records will be retained for 25 years. Records will be kept to enable linkage of participants' identity to CRF data (master log). This includes sufficient information from hospital and clinic records such as all original signed informed consent forms, source records, etc. After 25 years, all study records will be destroyed by shredding or incineration.

18.1. Distribution Records

The manufacturer of the medical device undergoing investigational testing in Canada must maintain distribution records as detailed under Sections 52 to 56 of Part 3 of the *Medical Device Regulations*.

Section 55 of the *Medical Device Regulations* requires the manufacturer to retain the distribution records maintained in respect of a medical device for the longer of:

a. the projected useful life of the device; or
b. two years after the date the device is shipped.

19. Publication Plan

The results of this study will be presented at the Canadian Critical Care Forum, a peer reviewed international meeting for critical care professional. The main findings will be published in a peer-reviewed journal and presented at peer-reviewed meetings.

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