

**Supplementary file to:****DirEct Versus Video LaryngosCope (DEVICE): Protocol and statistical analysis plan for a randomized clinical trial**

## Table of Contents

1. SPIRIT 2013 Checklist
2. List of DEVICE Investigators
3. Definition of ICU-Free Days (ICU-FDs)
4. Definition of Ventilator-Free Days (VFDs)
5. Safety Monitoring and Adverse Events
  - 5.1. Adverse Event Definitions
  - 5.2. Monitoring for Adverse Events
  - 5.3. Recording and Reporting Adverse Events
  - 5.4. Clinical Outcomes that may be Exempt from Adverse Event Recording and Reporting
  - 5.5. Unanticipated Problems involving Risks to Subjects or Others
6. Patient Privacy and Data Storage
7. Plan for Communication of Protocol Changes

## 1. SPIRIT 2013 Checklist



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___1___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___6___
	2b	All items from the World Health Organization Trial Registration Data Set	___n/a___
Protocol version	3	Date and version identifier	___n/a___
Funding	4	Sources and types of financial, material, and other support	___29___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1-2, Supplement section 2_
	5b	Name and contact information for the trial sponsor	___29___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___29___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___11, 18, 29___

### Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____ 8-10 _____
	6b	Explanation for choice of comparators	_____ 8 _____
Objectives	7	Specific objectives or hypotheses	_____ 10 _____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____ 11 _____
<b>Methods: Participants, interventions, and outcomes</b>			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____ 5, 23 _____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____ 11 _____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____ 12-13 _____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____ 13 _____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____ 13-14 _____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____ 13 _____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____ 16-18 _____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____ 30 _____

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____ 18 _____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____ n/a _____

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____ 11-12 _____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____ 11-12 _____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____ 11-12 _____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____ 12 _____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____ n/a _____

### Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____ 13-18 _____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____ 13, 16, 19 _____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	___35___
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___19-22___
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___21, 23___
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___23___
<b>Methods: Monitoring</b>			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___18___
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___18___
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___Supplement section 5___
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___18-19___
<b>Ethics and dissemination</b>			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___23-24___
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___Supplement section 7___
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___23-25___

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__ Supplement section 6 ____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__ Supplement section 6 ____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____ 29 ____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__ Supplement section 6 ____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	____ n/a ____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____ 10, 25 ____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____ n/a ____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__ Supplement section 6 ____
<b>Appendices</b>			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____ n/a ____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____ n/a ____

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons [“Attribution-NonCommercial-NoDerivs 3.0 Unported”](https://creativecommons.org/licenses/by-nc-nd/3.0/) license.

## 2. List of DEVICE Investigators

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University of Colorado School of Medicine– Daniel Resnick-Ault, MD\*; Jill J. Bastman, BSN, RN\*; Adit A. Ginde, MD, MPH\*; Cori Withers, BS.

University of Alabama at Birmingham Medical Center and Heersink School of Medicine– Derek W. Russell, MD\*; Sheetal Gandotra, MD\*; Sarah W. Robison, MD\*; Micah R. Whitson, MD\*; David B. Page, MD, MSPH\*; Anna Altz-Stamm RN, BSN, CCRN; Mary Clay Boone RN, BSN; Robert B. Johnson RRT; Geri-Anne Warman RN, BSN; Jennifer J. Oswald RN, BSN; Jerrod Isbell RRT; Anne Merrill Mason RN, BSN; Gina White RN, BSN; Drew Robinson MD; Jordan Minish MD; Reed Lahaye MD; Edwin Gunn MD; Abdulhakim Tlimat MD; Tyler Greathouse DO; Luis L. Tatem MD; Christopher Richardson MD; Austin Oslock MD; John Patrick Simmons MD; Morgan Locy MD, PhD; Ryan Goetz MD; Daniel Sullivan MD; Ross Schumacher MD; Melissa Jordan MD; Jonathan Kalehoff MD; Anneka Hutton MD; Daniel Kelmenson MD; Meena Sridhar MD; Ahmed Salem MD; Aneesah B. Jaumally MD; Ishan Lalani MD, MPH; William S. Stigler

MD; Phillip J. O'Reilly MD; Donna S. Harris RN, BSN; Cara E. Porter RN, ADN; Sonya Hardy, MA; Puneet Aulakh MD; Joseph B. Barney MD; Joseph Chiles III MD; Bryan Garcia MD; Aditya Kotecha MD; Takudzwa Mkorombindo MD; Peter Morris MD; Kinner Patel MD; R. Chad Wade MD; Carla Copeland MD; Michael C. Kurz, MD, MS.

Denver Health Medical Center– Stacy A. Trent, MD, MSPH\*; Ivor S. Douglas, MD\*; Carol Lynn Lyle, PA-C, MPH.

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### 3. Definition of ICU-Free Days (ICU-FDs)

ICU-FDs are defined as the number of days, between enrollment and 28 days after enrollment, in which the patient is alive and not admitted to an intensive care unit service after the patient's final discharge from the intensive care unit. Patients who are never discharged from the intensive care unit receive a value of 0. Patients who die before day 28 receive a value of 0. For patients who return to an ICU and are subsequently discharged prior to day 28, ICU-free days are counted from the date of final ICU discharge. All data are censored hospital discharge or 28 days, whichever comes first.

#### **4. Definition of Ventilator-Free Days (VFDs)**

VFDs are defined as the number of days, between enrollment and 28 days after enrollment, during which the patient is alive and with unassisted breathing and remains free of assisted breathing. If a patient returns to assisted breathing and subsequently achieves unassisted breathing prior to day 28, VFD will be counted from the end of the last period of assisted breathing to day 28. If the patient is receiving assisted ventilation at day 28 or dies prior to day 28, VFDs are 0. If a patient is discharged while receiving assisted ventilation, VFDs are 0. All data is censored hospital discharge or 28 days, whichever comes first.

## 5. Safety Monitoring and Adverse Events

Assuring patient safety is an essential component of this protocol. Use of a video laryngoscope and use of a direct laryngoscope are both standard-of-care interventions that have been used in clinical practice for decades with an established safety profile. However, any trial conducted during a high-risk, time-sensitive procedure like tracheal intubation of critically ill patients raises unique safety considerations. This protocol addresses these considerations through:

1. Exclusion criteria designed to prevent enrollment of patients likely to experience adverse events from intubation using a video laryngoscope or intubation using a direct laryngoscope;
2. Systematic collection of outcomes relevant to the safety of intubation using a video laryngoscope or intubation using a direct laryngoscope;
3. Structured monitoring, assessment, recording, and reporting of adverse events.

### 5.1. Adverse Event Definitions

*Adverse Event* – An adverse event will be defined as any untoward or unfavorable medical occurrence in a human subject temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Any adverse event occurring during the research will be classified according to the following characteristics:

- *Seriousness* – An adverse event will be considered “serious” if it:
  - Results in death;
  - Is life-threatening (defined as placing the patient at immediate risk of death);
  - Results in inpatient hospitalization or prolongation of existing hospitalization;
  - Results in a persistent or significant disability or incapacity;
  - Results in a congenital anomaly or birth defect; or

- Based upon appropriate medical judgment, may jeopardize the patient's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.
- *Unexpectedness* – An adverse event will be considered “unexpected” if the nature, severity, or frequency is neither consistent with:
  - The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in the protocol-related documents, such as the IRB-approved research protocol; nor
  - The expected natural progression of any underlying disease, disorder, or condition of the subject experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.
- *Relatedness* – The strength of the relationship of an adverse event to a study intervention or study procedure will be defined as follows:
  - Definitely Related: The adverse event follows (1) a reasonable, temporal sequence from a study procedure AND (2) cannot be explained by the known characteristics of the patient's clinical state or other therapies AND (3) evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedures.
  - Probably or Possibly Related: The adverse event meets some but not all of the above criteria for “Definitely Related”.
  - Probably Not Related: The adverse event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.
  - Definitely Not Related: The adverse event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.

- Uncertain Relationship: The adverse event does not fit in any of the above categories.

## 5.2. Monitoring for Adverse Events

The time interval during which patients will be monitored for the occurrence of adverse events begins at randomization and ends at the first of hospital discharge or 28 days. Adverse events occurring before randomization or after hospital discharge or 28 days will not be collected. The lead investigator at each enrolling site will have primary responsibility for overseeing the monitoring, assessment, and reporting of adverse events. Site study personnel will evaluate for the occurrence of adverse events by manual review of the electronic health record and by communication with treating clinicians. Site study personnel will evaluate for the occurrence of adverse events by manual review of the electronic health record at two time points. The first will occur as close as feasible to 24 hours after randomization during initial data collection. The second will occur at the first of hospital discharge or 28 days after enrollment during final data collection. Study personnel at each site will also communicate regularly with the treating clinicians who perform tracheal intubation in the study environments between enrollment and 28 days after enrollment to solicit information about any potential adverse events. If study personnel at a site identify a potential adverse event, the lead investigator at the site will be immediately notified. The lead investigator at the site will assess the seriousness, unexpectedness, and relatedness of the potential adverse event. With assistance as needed from the coordinating center and the trial primary investigator, the lead investigator at the site will determine whether the event qualifies for recording and reporting.

## 5.3. Recording and Reporting Adverse Events

The following types of adverse events will be recorded and reported:

- Adverse events that are Serious and Definitely Related, Probably or Possibly Related, or of Uncertain Relationship.
- Adverse events that are Unexpected and Definitely Related, Probably or Possibly Related, or of Uncertain Relationship.

Adverse events that do not meet the above criteria will not be recorded or reported. Adverse events that the lead investigator at a site assesses to meet the above criteria for recording and reporting will be entered into the adverse event electronic case report form in the trial database. The lead investigator at the site will record an assessment of each characteristic for the adverse event, including seriousness, unexpectedness, and relatedness. For any adverse event that is **serious AND unexpected**, and definitely related, probably or possibly related, or of uncertain relationship, the lead investigator at the site will report the adverse event to the coordinating center and the trial primary investigators **within 24 hours** of becoming aware of the adverse event. For any other adverse event requiring recording and reporting, the lead investigator at the site will report the adverse event to the coordinating center and the trial primary investigators **within 72 hours** of becoming aware of the adverse event. The coordinating center and the trial principal investigator will coordinate with the lead investigator at the site to obtain information about the adverse event regarding each characteristic for the adverse event, including seriousness, expectedness, and relatedness. The lead investigator at the site will be responsible for making final determinations regarding seriousness and unexpectedness. The coordinating center and trial principal investigator will be responsible for making final determinations regarding relatedness.

For adverse events that meet the above criteria for recording and reporting, the coordinating center will notify the DSMB, the IRB, and the sponsor in accordance with the following reporting plan:

Characteristics of the Adverse Event	Reporting Period
Fatal or life-threatening (and therefore serious), unexpected, and definitely related, probably or possibly related, or of uncertain relationship.	Report to the DSMB, IRB, and sponsor within 7 days after notification of the event.
Serious but non-fatal and non-life-threatening, unexpected, and definitely related, probably or possibly related, or of uncertain relationship.	Report to DSMB, IRB, and sponsor within 15 days of notification of the event.
All other adverse events meeting criteria for recording and reporting.	Report to DSMB in regularly scheduled DSMB safety reports.

#### 5.4. Clinical Outcomes that may be Exempt from Adverse Event Recording and Reporting

In this study of critically ill patients at high risk for death and other adverse outcomes due to their underlying critical illness, clinical outcomes, including death and organ dysfunction, will be systematically collected and analyzed for all patients. The primary, secondary, safety, and exploratory outcomes will be recorded and reported as clinical outcomes and not as adverse events unless treating clinicians or site investigators believe the event is Definitely Related or Probably or Possibly Related to the study intervention or study procedures. This approach – considering death and organ dysfunction as clinical outcomes rather than adverse events and systematically collecting these clinical outcomes for analysis – is common in ICU trials. This approach ensures comprehensive data on death and organ dysfunction for all patients, rather than relying on sporadic adverse event reporting to identify these important events. The following events are examples of study-specific clinical outcomes that would not be recorded



and reported as adverse events unless treating clinicians or site investigators believe the event was Definitely Related or Probably or Possibly Related to the study intervention or study procedures:

- Death (all deaths occurring prior to hospital discharge or 28 days will be recorded);
- Organ dysfunction
  - Pulmonary – hypoxemia, aspiration, acute hypoxemic respiratory failure, pneumothorax
  - Cardiac – hypotension, shock, vasopressor receipt, cardiac arrest;
- Duration of mechanical ventilation;
- Duration of ICU admission;
- Duration of hospitalization

Note: A study-specific clinical outcome may also qualify as an adverse event meeting criteria for recording and reporting. For example, an injury to the teeth that the investigator considers Definitely Related to randomization to use of a direct laryngoscope would be both recorded as a study-specific clinical outcome and recorded and reported as a Serious and Definitely Related adverse event.

### **5.5. Unanticipated Problems Involving Risks to Subjects or Others**

Investigators must also report Unanticipated Problems Involving Risks to Subjects or Others (“Unanticipated Problems”), regardless of severity, associated with study procedures within 24 hours of the site investigator becoming aware of the Unanticipated Problem. An Unanticipated Problem is defined as any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol; and (b) the characteristics of the subject population being studied; AND
- Definitely Related or Probably or Possibly Related to participation in the research (as defined above in the section on characteristics of adverse events); AND
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If any study personnel at a site become aware of an event that may represent an Unanticipated problem, they will immediately contact the lead investigator for the site. The lead investigator at the site will assess whether the event represents an Unanticipated Problem by applying the criteria described above. If the lead investigator at the site determines that the event represents an Unanticipated Problem, the lead investigator at the site investigator will record the Unanticipated Problem in the Unanticipated Problem electronic case report form in the trial database. The lead investigator at the site will then communicate that an Unanticipated Problem has occurred to the coordinating center and the trial principal investigator within 24 hours of the lead investigator at the site becoming aware of the Unanticipated Problem. The coordinating center and principal investigator will coordinate with the lead investigator at the site to obtain information about the Unanticipated Problem. The coordinating center will report the Unanticipated Problem to the DSMB, IRB, and sponsor within 15 days of becoming aware of the Unanticipated Problem.

## 6. Patient Privacy and Data Storage

At no time during this study, its analysis, or its publication, will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities or other private healthcare information (PHI), is collected. All subjects are assigned a unique study ID number for tracking purposes. Data collected from the medical record is entered into the secure online database REDCap. The PHI required to accurately collect clinical and outcomes data is available only to investigators at the site at which the subject is enrolled, and this data is shared only in completely de-identified form with the coordinating center via the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event are stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. The de-identified dataset housed in REDCap will be accessed by the coordinating center for reporting the results of this trial. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, all PHI at local centers will be expunged and only the de-identified version of the database will be retained. Potential future use of de-identified data generated in the course of this study by the coordinating center and other participating sites is allowed and will be governed by mutual data sharing use agreements.

## 7. Plan for Communication of Protocol Changes

Any changes to the trial protocol (e.g., changes to eligibility criteria, outcomes, analyses) will be implemented via a new version of the full trial protocol, tracked with the date of the update and the version number of the trial protocol. A list summarizing the changes made with each protocol revision will be included at the end of each protocol. The updated protocol will be sent to the relevant IRBs for tracking prior to implementation of the protocol change. At the time of publication, the original trial protocol, and the final trial protocol, including the summary of changes made with each protocol change, will be included in the supplementary material for publication.