Supplemental Materials

Contents

Standard Protocol Items for Randomized Trials (SPIRIT) 2013 Checklist

Section/item	Item No	Ms Pg	Description
Administrative information			
Title	1	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	5	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	1-27	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	23-24	Date and version identifier
Funding	4	2	Sources and types of financial, material, and other support
Roles and responsibilities	5a	1	Names, affiliations, and roles of protocol contributors
	5b	2	Name and contact information for the trial sponsor
	5c	2	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
	5d	2	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)
Introduction			
Background and rationale	6a	6-8	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of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	8	Explanation for choice of comparators
Objectives	7	8	Specific objectives or hypotheses
Trial design	8	9	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes			
Study setting	9	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
Eligibility criteria	10	9-10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	12-14	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	22	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)
	11c	22	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

	11d	15-17	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	18-19	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
Participant timeline	13	10,39	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	10	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	10	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions			
Allocation:			
Sequence generation	16a	11	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
Allocation concealment mechanism	16b	11	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
Implementation	16c	11	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	11-12	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	11-12	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis			
Data collection methods	18a	21	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
	18b	21-22	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
Data management	19	21	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
Statistical methods	20a	24-25	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
	20b	25-26	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	25	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring			
Data monitoring	21a	23	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
	21b	23	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
Harms	22	23	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	21	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination			
Research ethics approval	24	27	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	23-24	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)
Consent or assent	26a	10	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b		Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	21	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
Declaration of interests	28	2	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	10	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
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
Dissemination policy	31a	27	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
	31b	32	Authorship eligibility guidelines and any intended use of professional writers
	31c		Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices			
Informed consent materials	32		Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	S17	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

*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" license.

From: Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200-7.

Appendix A: Calculation of Norepinephrine Equivalents

Norepinephrine equivalents for the purposes of trial exclusion criteria are calculated according the conversion factors outlined below.

Vasopressor	Range of ratios	Suggested ratio	Equivalent dose
Norepinephrine	1	1	0.1 mcg/kg/min
Epinephrine	0.7-1.4	1	0.1 mcg/kg/min
Dopamine	75.2-144.4	100	10 mcg/kg/min
Metaraminol	8.3	8	0.8 mcg/kg/min
Phenylephrine	1.1-16.3	10	1 mcg/kg/min
Vasopressin	0.3-0.4	0.4	0.04 units/min
Angiotensin II	0.07-0.13	0.1	0.01 mcg/kg/min

Ratios are reported in reference to 1 unit of norepinephrine. For calculations, all doses are in mcg/kg/min with the exception of vasopressin in units/min. Angiotensin II is usually dosed in ng/kg/min and must be converted to mcg/kg/min for calculations.

From: Goradia S, Sardaneh AA, Narayan SW, Penm J, Patanwala AE. Vasopressor dose equivalence: A scoping review and suggested formula. *J Crit Care*. 2021;61:233-240.

Appendix B: SAT/SBT and Wake-Up Test Safety Screen

Eligibility: Patients are candidates if they are on mechanical ventilation.

Step 1: Spontaneous Awakening Trial (SAT) Safety Screen (pass/fail)

If the patient has any of the following criteria, he/she fails the safety screen and should not have an SAT at that time. The SAT safety screen criteria include the following:

- Active seizures: the patient is currently receiving medications for active seizures;
- Alcohol withdrawal: the patient is currently receiving medications for alcohol withdrawal;
- Agitation: the patient is currently or has recently (in the last 2 hours) receiving medications for agitation (Richmond Agitation Sedation Scale [RASS] ≥2);
- Neuromuscular blocking drugs: the patient is currently on a neuromuscular blocking drug infusion;
- Myocardial ischemia: documentation of myocardial ischemia in the last 24 hours;
- High intracranial pressure: there is evidence of elevated intracranial pressure (>20 mmHg); and
- Patient off the unit: effort should be made to attempt the safety screen when the patient returns to unit.

If the patient does not pass the SAT safety screen, it is not considered safe to turn off the sedatives. No further action is needed. Bedside staff should try the safety screen again in 24 hours; bedside staff can reassess safety criteria before 24 hours if the patient's condition has changed and bedside staff or the clinical team think the patient would pass the safety screen.

If the patient passes the SAT safety screen, perform the SAT.

Step 2: Perform the SAT

The SAT is defined as the discontinuation of all sedatives being given for sedation; administration of medications being used for the purpose of analgesia should continue. The SAT failure criteria include the following:

- Sustained anxiety or agitation;
- Respiratory rate >35 breaths/minute for 5 minutes;
- Peripheral capillary oxygen saturation (SpO_2) <88% for 5 minutes;
- Respiratory distress; and
- Acute cardiac dysrhythmia.

SAT pass criteria include the following:

- The patient opens their eyes to voice (RASS ≥-3) and is tolerating sedative cessation for any amount of time; or
- The patient is comatose and tolerating sedative cessation for >4 hours.

If the patient fails the SAT, bedside staff should restart at the lowest possible infusion rate that is needed to achieve target RASS. Typically start at half of the most recent dose and titrate, as needed.

If the patient passes the SAT, then he/she exhibits either of the pass criteria and no failure criteria, and he/she advances to the spontaneous breathing trial (SBT) safety screen.

Step 3: Spontaneous Breathing Trial (SBT) Safety Screen (pass/fail)

If the patient has any of the following criteria, he/she fails the safety screen and should not have an SBT at that time. The SBT safety screen criteria include the following:

- Agitation: the patient is currently agitated (RASS $\geq$ 2);
- Oxygen saturation <88%;
- Fraction of inspired oxygen (FiO_2) >50%;
- Positive end-expiratory pressure (PEEP) >7.5 cmH_2O;
- Myocardial ischemia: documentation of myocardial ischemia in the last 24 hours;
- Vasopressor use: the patient has documented significant use of vasopressors, including the following:
    - Dopamine or dobutamine infusion >5 mcg/kg/minute;
    - Norepinephrine or epinephrine infusion >2 mcg/minute; or
    - Vasopressin or milrinone at any dose.
- Patient off the unit: effort should be made to attempt the safety screen when the patient returns to the unit.

If the patient fails the SBT safety screen, bedside staff should try the safety screen again within 24 hours. Bedside staff can reassess safety criteria before 24 hours if the patient remains off sedatives, his/her condition has changed, and bedside staff or the clinical team think the patient would pass the safety screen.

If the patient passes the SBT safety screen, perform SBT.

Step 4: Perform the SBT

The SBT is defined as discontinuation of active ventilator support so that the patient is allowed to breathe through a T-tube circuit or the ventilator circuit with continuous positive airway pressure (CPAP)/PEEP $\leq$7.5 cmH_2O and pressure support of $\leq$7 cmH_2O. The SBT failure criteria include the following:

- Sustained respiratory rate >35/minute;
- Sustained respiratory rate <8/minute;
- Sustained SpO_2 <88%;
- Respiratory distress;
- Mental status change; or
- Acute cardiac arrhythmia

If the patient fails the SBT, bedside staff should return the ventilatory support to the previous settings.

If the patient passes the SBT, defined as the patient exhibiting no failure criteria for 2 hours, at the end of the 2 hours the clinical team should consider extubation.

Appendix C: Per-Protocol Rescue Sedation

Inadequate sedation should first be addressed through titration of the study drug and treatment of pain, where applicable, per the standard of care. If sedation remains inadequate despite adequate analgesia, per-protocol rescue sedation is stepwise:

First-line rescue: bolus doses of the assigned study sedative drug	
Propofol: 0.3 to 0.5 mg/kg	A maximum of two bolus doses per hour are allowed before use of second-line sedatives
Isoflurane: 0.3 to 0.5 ml	
Second-line rescue: rescue sedatives when the study drug is insufficient	
Dexmedetomidine infusion: 0.15 to 0.7 mcg/kg/hour for up to 3 hours per 24 hour period; and/or	
Midazolam bolus: 0.5 to 5 mg per dose, up to 3 bolus doses per 24 hour period	
Treatment failure criteria	
Clinical need for dexmedetomidine infusion for >3 hours per 24 hours; and/or	
Clinical need for >3 midazolam bolus doses per 24 hours	

Patients meeting criteria for treatment failure should, as soon as possible, discontinue the assigned study drug and transition to medical care per the standard of care at the discretion of the treating physician.

Appendix D: Prohibited and Restricted Medications

Prohibited medications
Barbiturates
Chloral hydrate
Chlorpromazine
Clonidine
Gamma-hydroxybutyrate
Ketamine
Continued treatment with a neuromuscular blocking agent for >4 hours during the study drug treatment period
Restricted Medications
Propofol: non-study drug propofol infusions are not permitted in either of the treatment arms for sedation with the exception of procedures inside or outside the ICU
Benzodiazepines (i.e., midazolam): may only be used as rescue sedatives if study sedation is not sufficient
α2-adrenergic agonists (i.e., dexmedetomidine): may only be used as rescue sedatives if study sedation is not sufficient and during spontaneous awakening trials and the wake-up test
Antipsychotics (e.g., haloperidol, quetiapine, olanzapine, and chlorpromazine): should not be used during study sedation treatment period unless the patient has been on these medications before ICU admission, except during spontaneous awakening trials, and during the end of treatment wake-up test
Neuromuscular blocking agents: continuous infusions of neuromuscular blocking agents during the study drug sedation treatment period for >4 hours are not permitted. Shorter infusions of NMBA may be used as indicated for medical procedures.

Appendix E: Other secondary and exploratory outcomes

Other secondary outcomes
Time from end of treatment to extubation if the study drug is terminated for extubation
Days alive and free from mechanical ventilation through study day 30[1]
Days alive and free from the ICU through study day 30[2]
Delirium and coma free days from the start of the study drug until 7 days after end of treatment, as assessed by CAM-ICU-7 and RASS
Mortality rate at 30 days after randomization
Mortality rate 3 months after randomization
Mortality rate at 6 months after randomization
Proportion of patients receiving restraints during the study drug treatment period
Safety of isoflurane versus propofol
Frequency and type of Sedaconda ACD-S device deficiencies
Exploratory outcomes
Changes in isoflurane dose over time
Incidence of major ICU interventions through study day 30 or until ICU discharge: renal replacement therapy, extracorporeal life support, tracheostomy, and non-invasive ventilation
Level of care up to 30 days after randomization
End-tidal isoflurane concentration over time and relation to RASS
Oxygenation (PaO_2/FiO_2) in patients with ARDS/AHRF over time during the treatment period
Use of rescue sedatives, other sedatives, and antipsychotics from randomization to end of treatment
Change from baseline in highest daily vasoactive drug requirements during study drug treatment
Duration of mechanical ventilation
ICU length of stay
Change in minute ventilation every 8 hours during the study drug treatment period
Exploratory long-term outcomes
Number of factual memories, memories of feelings, or delusional memories, as assessed by the ICU Memory Tool, collected at 3 months follow-up
Activities of daily living, as assessed by the Katz ADL and Pfeffer FAQ, at 3 and 6 months post randomization
Depression, anxiety, and post-traumatic stress symptoms, as assessed by IES-R and PROMIS Depression and Anxiety questionnaires, at 3 and 6 months post randomization
Cognitive function, as assessed by TICS, WAIS IV Digit Span, Hayling Sentence Completion Test, Controlled Oral Word Association, WMS IV – Immediate Memory (Adult/Older Adult), WMS IV – Delayed Memory (Adult/Older Adult), and PROMIS Cognitive Function questionnaire, at 3 and 6 months post randomization
Quality of life at 3 and 6 months post-randomization, as assessed by WHODAS 2.0 and BPI

[1] For days alive and free from mechanical ventilation, only invasive ventilation is considered. Successful mechanical ventilator discontinuation is defined as being alive and free from mechanical ventilation for ≥ 48 hours following discontinuation. For example, if a patient was liberated from mechanical ventilation, and mechanical ventilation was initiated again within the next 48 hours, or the patient died within the next 48 hours, criteria would not be met for that that time (which is less than 48 hours) to count toward days alive and free from mechanical ventilation.

[2] Days alive and free from the ICU is defined similarly to the days alive and free from mechanical ventilation. Successful ICU discharge is defined as being alive and out of the ICU for ≥ 48 hours following discharge.

ACD-S, Anaesthetic Conserving Device - S; AHRF, acute hypoxemic respiratory failure; ARDS, acute respiratory distress syndrome; BPI, Brief Pain Inventory; CAM-ICU-7, Confusion Assessment Method Intensive Care Unit-7; FiO2, fraction of inspired oxygen; ICU, intensive care unit; IES-R, impact of event scale; Katz ADL, Katz Index of Independence in Activity of Daily Living; PaO_2, arterial partial pressure of oxygen; Pfeffer FAQ, Pfeffer Functional Activities Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RASS, Richmond Agitation Sedation Scale; TICS, Telephone Interview for Cognitive Status; WAIS, Wechsler adult intelligence scale; WHODAS 2.0, World Health Organization Disability Assessment Schedule 2.0; WMS, Wechsler memory scale

Appendix F: Exclusionary Periods for Blinded RASS and CPOT Assessments

Blinded Richmond Agitation Sedation Scale (RASS) and Critical Care Pain Observation Tool (CPOT) assessments will not be performed during or shortly after periods of intentional deepening of sedation for procedures, nor during a spontaneous awakening trial (SAT). The earliest blinded RASS and CPOT assessments allowed after intentional changes in sedation level are as follows:

1 hour after intentional deepening of sedation for an in-ICU procedure (e.g., following bronchoscopy, prone-positioning, or wound dressing)
1 hour after resuming study sedation after a procedure outside the ICU (e.g., CT scan, endoscopy, surgery, etc.)
1 hour after an SAT
2 hours after a bolus of neuromuscular blocking agent
4 hours after the end of an infusion of neuromuscular blocking agent

If a clinical event meets more than one scenario with different exclusion periods, then the longer time period applies. For example, a patient who undergoes a procedure outside the ICU that requires neuromuscular blocking agent (NMBA) infusion would have no blinded assessments done for 4 hours after the end of the NMBA. After the excluded period, blinded assessments should resume per the original schedule.

Appendix G: Criteria for Early Study Drug Discontinuation and Study Withdrawal

Criteria for early study drug discontinuation
Treatment failure (i.e., clinical failure of the patient to be adequately sedated with the study drug)
New onset of coma due to structural brain disease (e.g., stroke, intracranial hemorrhage, cranial trauma, malignancy, anoxic brain injury, or cerebral edema)
Severe or serious adverse events: - Development of an adverse event of special interest that qualifies as a severe adverse event or serious adverse events at least possibly related to study drug, without a clear alternate explanation; - For any other severe adverse events, the decision on whether to continue with study drug will be made by the investigator and clinical team in accordance with whether continuation/reintroduction of study drug is in the best interest of the patient for the first severe adverse event; or - A second severe adverse event or any serious adverse event without a clear alternate explanation will lead to discontinuation of study treatment
Unresolved Sedaconda ACD-S device-related issues
Transition to comfort care
Death
Requirement of prohibited concomitant medication
Need for ECMO, $ECCO_2R$, HFOV, or HFPV
Any medical condition that indicates to the investigator that continued study drug treatment is not in the best interest of the patient
Withdrawal of consent to receive study drug
Criteria for study withdrawal
Any medical condition that indicates to the investigator that continued participation is not in the best interest of the patient
Withdrawal of consent by the patient or legally authorized representative, or request for discontinuation from the study for any reason
Withdrawal of the site by the sponsor due to investigator failure to comply with protocol requirements or study-related procedures
Termination of the study by the Sponsor or the regulatory authority

ACD-S, Anaesthetic Conserving Device – S; $ECCO_2R$, extracorporeal CO2 removal; ECMO, extracorporeal membrane oxygenation; HFOV, high frequency oscillation ventilation; HFPV, high frequency percussive ventilation

Appendix H: Adverse Events of Special Interest

AESI	Severity			
	Mild	**Moderate**	**Severe**	**Serious**
Hypoxemia	Oxygen desaturation event that requires an increase in FiO_2 of >10% or any increase in PEEP for >60 minutes to maintain SpO_2 of at least 88%, despite ventilator optimization.	Oxygen desaturation event that requires an increase in FiO_2 >20% or increase in PEEP of >5 cmH_2O for >60 minutes to maintain SpO_2 of at least 88%, despite ventilator optimization.	Refractory hypoxemia, defined as SpO_2 <88% lasting for 30 minutes or longer, despite ventilator optimization.	Need for respiratory rescue therapy, defined as ECMO, $ECCO_2R$, inhaled nitric oxide, or inhaled epoprostenol initiated for life threatening refractory hypoxemia, or other life-threatening manifestations of hypoxemia.
Hypercapnia	$PaCO_2$ 10 to 15 mmHg above baseline on 2 consecutive blood gases at least 60 minutes apart, despite ventilator optimization.	$PaCO_2$ 16 to 20 mmHg above baseline on 2 consecutive blood gases at least 60 minutes apart, despite ventilator optimization.	$PaCO_2$ >20 mmHg above baseline on 2 consecutive blood gases at least 60 minutes apart, despite ventilator optimization.	ECMO support or life-threatening manifestations of respiratory acidosis.
Malignant hyperthermia				Any episode of MH.[1]
Propofol-related infusion syndrome suspected by the investigator in a patient recently exposed to propofol				Any episode of PRIS.[2]
Accidental self-extubation	Accidental self-extubation will be recorded as an AESI, but grading is unnecessary, per FDA guidance.			
Hypotension	New episode of SBP <90* mmHg or MAP <65* mmHg lasting at >60 minutes **OR** fluid bolus ≥1000 mL over <60 minutes **OR** new low dose vasopressor <0.05 mcg/kg/min norepinephrine equivalent >60 minutes **OR** increase of existing vasopressor by 0.05 to 0.1 mcg/kg/min norepinephrine equivalent over from baseline and increase lasting >60 minutes.	New low dose vasopressor 0.05 to <0.2 mcg/kg/min norepinephrine equivalent OR increase over <60 minutes of vasopressor(s) by 0.1 to <0.2 mcg/kg/min norepinephrine equivalent and lasting >60 minutes, to maintain SBP ≥90* mmHg or MAP ≥65* mmHg.	New vasopressor ≥0.2 mcg/kg/min norepinephrine equivalent or increase over <60 minutes of vasopressor(s) by ≥0.2 mcg/kg/min norepinephrine equivalent and lasting >60 minutes, to maintain SBP ≥90* mmHg or MAP ≥65* mmHg.	Immediate life-threatening hypotension, requiring intervention (e.g., CPR, mechanical circulatory support).

Liver injury	1) ALT ≥3 × ULN; or 2) AST ≥3 × ULN; or 3) Total bilirubin >2 × ULN; or 4) Alkaline phosphatase >2 × ULN.	Hy's Law criteria (ALT or AST 3 × ULN and total bilirubin >2 × ULN).	Mild encephalopathy and Hy's Law criteria (ALT or AST 3 × ULN and total bilirubin >2 × ULN).	Life-threatening consequences; moderate to severe encephalopathy; coma and Hy's Law criteria (ALT or AST >3 × ULN and total bilirubin >2 × ULN).
Hyperkalemia	>5.5 mEq/L (>5.5 mmol/L) in a non-hemolyzed sample and in absence of respiratory acidosis.	>6.0 to 6.5 mEq/L (6.0 to 6.5 mmol/L) in a non-hemolyzed sample for which a medication or dialysis to lower potassium was prescribed.	>6.5 to 7.0 mEq/L (>6.5 to 7.0 mmol/L) in a non- hemolyzed sample for which a medication or dialysis to lower potassium was prescribed.	>7.0 mEq/L (>7.0 mmol/L) in a non-hemolyzed sample for which a medication or dialysis to lower potassium was prescribed, or life-threatening arrhythmia due to hyperkalemia.
Rhabdomyolysis independent of malignant hyperthermia	CK 10,000 to 20,000 units/L	CK >20,000 units/L with moderate renal failure graded as AKIN Stage 3.[3]	CK >20,000 units/L requiring dialysis.	Life-threatening consequences of rhabdomyolysis.

* Unless a different clinical target is selected by the clinical team prior to randomization.

[1] MH may be characterized by muscle rigidity; unexplained hypercapnia resistant to increasing minute ventilation; elevated CK or urine myoglobin suggesting rhabdomyolysis; acute hyperkalemia >6 mEq/L potentially resulting in ECG changes of peaked T waves, increased ventricular tachycardia, or ventricular fibrillation and hyperthermia in a patient exposed to volatile anesthetic or succinylcholine.

[2] PRIS may be characterized by the development of otherwise unexplained metabolic acidosis and cardiac dysfunction with at least one of the following: rhabdomyolysis, hypertriglyceridemia, or renal failure after initiation of propofol.

[3] Lopes JA, Jorge S. The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review. *Clin Kidney J*. 2013;6(1):8-14.

AESI, adverse event of special interest; AKIN, Acute Kidney Injury Network; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CPR, cardiopulmonary resuscitation; $ECCO_2R$, extracorporeal carbon dioxide removal; ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; FDA, Food and Drug Administration; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; MH, malignant hyperthermia; $PaCO_2$, arterial partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure; PRIS, propofol-related infusion syndrome; SBP, systolic blood pressure; SpO_2, peripheral capillary oxygen saturation; ULN, upper limit of normal.

Appendix I: Study Stopping Criteria

Criteria in the isoflurane group triggering an ad hoc data safety monitoring board meeting:

Occurrence of moderate or severe adverse events related to isoflurane or the device	Events observed in the isoflurane group
Serious adverse event – death	>1 patient
Serious adverse event	≥5 patients
Suspected unexpected serious adverse reaction	≥3 patients
Malignant hyperthermia	>2 patients
Hypoxemia – moderate	>10 patients
Hypoxemia – severe	>5 patients
Hypercapnia – moderate	>10 patients
Hypercapnia – severe	>5 patients
Accidental self-extubation	≥10 patients
Hypotension – moderate	>10 patients
Hypotension – severe	>5 patients
Drug-induced liver injury – moderate and severe	≥2 patients
Hyperkalemia – moderate	>10 patients
Hyperkalemia – severe	>5 patients
Rhabdomyolysis independent of malignant hyperthermia – moderate	≥5 patients
Rhabdomyolysis independent of malignant hyperthermia – severe	≥2 patients

Definitions and grading of each AE of special interest are described in the preceding appendix.

If >5 reports of suspected unexpected serious adverse reactions concerning the same type of medical event (i.e., unlabeled events with a suspected relationship to treatment), there will be an ad hoc data safety monitoring board meeting.

Appendix J: Informed Consent Materials

Protocol: Title:	A Phase 3, Multicenter, Randomized, Controlled, Open Label, Assessor-Blinded Study to Evaluate the Efficacy and Safety of Inhaled Isoflurane Delivered via the Sedaconda ACD-S Compared to Intravenous Propofol for Sedation of Mechanically Ventilated Intensive Care Unit Adult Patients (INSPiRE-ICU1)
Protocol No.:	SED003
Sponsor:	Sedana Medical AB, which is providing financial support and material for this study.
Principal Investigator: (Study Doctor)	[Insert Principal Investigator name and address]
24-hr. Telephone #:	[Insert 24-h phone number]
Address:	[Insert Site Location and address]

This form is for use in a research study that involves participants who may or may not have the capacity to take part in the study. In this document, "you" generally refers to the research participant. If you are being asked as the legally authorized representative (LAR) to permit the participant to take part in this research, "you" in the remainder of this consent form, refers to the research participant. During the course of the study, if the participant regains the capacity to consent, informed consent will be sought from the participant, and the participant will be offered the ability to leave the study if desired.

Why are you being asked to participate in this research study?

You are being invited to take part in a research study. Before agreeing, it is important that you read and understand why this research is being done and what it will involve for you. This form describes the purpose, procedures, benefits, risks, discomforts, and precautions of the study. It also describes the alternative procedures that are available to you and your right to withdraw from the study at any time.

A member of the study staff will review this form with you and explain the study to you. Please read this form carefully and ask any questions you may have. You can discuss this information with your doctors, family, or anyone else you would like before making your choice.

What is the background and purpose of the study?

You are being asked to participate in this research study because you will likely be on a ventilator in the Intensive Care Unit (ICU) for more than 12 hours and require continuous sedation as part of your normal medical care. The ventilator is used to assist your breathing while sedation is used to keep you comfortable on the ventilator. Sedation can range from minimal sedation (drowsy and relaxed) to deep sedation (unconscious and not awakened by verbal stimulation).

Sedation is commonly achieved using medications such as propofol, dexmedetomidine, benzodiazepines, or opioids administered through an intravenous catheter (IV; a tube in your vein) into the bloodstream. These sedatives, given as part of your routine medical care, help to

maintain comfort and safety, but they can have side effects, including longer time to wake up, confusion, lower blood pressure and heart rate, and change in breathing pattern.

Another method to provide sedation involves breathing inhaled medications such as isoflurane through the ventilator. Isoflurane is commonly used to achieve deep sedation (anesthesia) during surgery, in the United States and around the world. It may allow faster wake-up, less need for pain medications, and earlier return to more normal breathing patterns when compared to IV sedation. Traditionally, isoflurane administration has required large, specialized equipment called an anesthesia machine, limiting its use to operating rooms. A small device, placed in the ventilator breathing circuit, was developed to permit administration of isoflurane without an anesthesia machine, enabling administration in the ICU environment. This adaptor, called the Sedaconda Anaesthetic Conserving Device - S (Sedaconda ACD-S) is approved for use in Europe, Australia, Canada, Japan, and other countries, and isoflurane via the Sedaconda ACD-S is routinely prescribed as sedation for ICU patients in these countries. Isoflurane delivered by the Sedaconda ACD-S is approved for ICU sedation in several European countries, including Germany and France, but is not currently approved in the United States. As such, the use of isoflurane for ICU sedation delivered by the Sedaconda ACD-S in this research study is considered investigational.

The purpose of this study is to compare the effects of inhaled isoflurane sedation delivered via the Sedaconda ACD-S with the standard of care IV sedative propofol.

Do you have to take part in the study?

Taking part in this research study is voluntary and entirely up to you. You will have to sign and date the consent page within this consent form to indicate you choose to take part. You may change your mind and withdraw without giving any reason, at any time. If you choose to not participate or you withdraw from the study, you will not lose any medical benefits to which you are entitled, and it will not have any effect on your future medical care. You may decide to stop taking part in the study at any time by notifying the study doctor in writing of your decision. If you have some unresolved health problems when you leave the study, the study doctor may, if you agree, need to collect information about your health until the problem resolves.

What are your other options should you decide not to take part in the study?

You do not need to take part in this study. If you do not participate, you will receive standard of care sedation as prescribed by your doctors.

How many people will be in the study and how long will you be in this study?

Approximately 300 participants will take part in this study at approximately 15 to 20 study hospitals in the United States. Approximately 15-25 patients will be enrolled at this site.

The study sedation period will be up to 54 hours and only as long as sedation is required. After 54 hours, the treating doctor will decide whether to continue or stop sedation. If sedation is continued, you will receive standard of care sedation as prescribed by your doctors. You will be monitored for up to 7 days or until you are discharged from the hospital, whichever happens first. After 1 month, data regarding your hospital course will be collected from your medical records. The study team may give you or your representative a call if additional information regarding your hospital course is needed. At approximately 3 and 6 months after end of study treatment, members of the study team from Vanderbilt University will call or videocall you to ask about your ability to think clearly, your quality of life, and your mobility and function. They will ask you questions about what you remember from your time in the ICU.

What will happen if you decide to be in this research study?

There are 3 stages to this study: Screening, Study Treatment Period, and Follow-Up.

Screening

If you agree to participate in this study, study staff will check to see if there is any reason you should not be in the study. Study staff will review and collect information about your medical history, surgical history, present health and any medications that you are currently taking. We will ask you or your family questions about your ability to think clearly, quality of life, and mobility and function. These questions will take about 5-10 minutes, and you or your family will not have to answer any questions that make you or them feel uncomfortable. A blood sample will be taken to determine baseline safety assessments. For females who could become pregnant, a pregnancy test will be taken if not previously done during your hospital stay. The study team will ask for your contact information (phone numbers, email, and address) so that we can reach you after you leave the hospital to ask about your recovery.

Study Treatment Period

You will be randomized (like a flip of a coin) to determine which study treatment you receive: inhaled isoflurane (administered via the Sedaconda ACD-S device) or propofol (administered via IV infusion) for sedation. You will have a 60% chance to receive isoflurane and a 40% chance to receive propofol.

The bedside clinical nurse, study doctor, and study staff will know the study treatment and the doses that you are given. If the study medication (either isoflurane or propofol) you receive does not have the desired effect, you may receive other approved standard of care medications to achieve the sedation level prescribed by the clinical team. The appropriate level of sedation to be targeted will be determined by your treating physician and clinical team, not study staff.

In case of procedures outside the ICU, study drug must be stopped. If you return to the ICU before 42 hours from starting the study drug treatment, the study drug treatment can be resumed. If you return to ICU later than 42 hours from start of study drug treatment, you should transition to standard of care sedation and medical care at the discretion of the treating physician.

Because this is a research study, the study treatment will be given to you only during the study sedation period and not after the study is over. You will not receive isoflurane for ICU sedation after the study period, but your doctors can choose to prescribe propofol or another routinely used sedative provided through the hospital after the study sedation period.

Propofol: If you are assigned to receive propofol, then propofol will be given through an IV directly into your vein.

Isoflurane: If you are assigned to receive isoflurane, then isoflurane will be administered via the Sedaconda ACD-S device, which connects between the ventilator and the breathing tube.

Monitoring: While you are sedated with study medication, study staff will closely monitor you, your overall health, and your ongoing medical care, including medications that you are receiving. Study staff will frequently evaluate your sedation level, comfort, breathing pattern, and assess for any confusion. Your sedation tubing may be covered to ensure these assessments are not influenced by knowledge of which study medication you are receiving.

Physical Examinations: physical examination including an evaluation of your general appearance and your vital signs will be measured (body temperature, oxygen saturation, heart rate and blood pressure).

Blood samples: Blood samples will be collected and analyzed by the hospital clinical laboratory for safety monitoring. When able, these samples will be drawn from your existing lines to minimize discomfort. The total amount of blood taken will be

approximately 60 mL (4 tablespoons). For comparison, a standard blood donation at a blood collection center is about 475 mL of blood (about 96 teaspoons/2 cups).

Study treatment duration: The study sedation period will last for up to 54 hours and only as long as sedation is required. After this time, the treating doctor will decide whether to continue or stop sedation. If sedation is continued, you will receive standard of care sedation as prescribed by your doctors. If you are ready to come off the ventilator before end of the study sedation period, study medication will be stopped, and the breathing tube will be removed. You will not be kept on a ventilator any longer than your treating doctors think is medically necessary.

Follow-Up

After the study medication stops, the study team will monitor how fast you wake up, assess your comfort level, evaluate for confusion, and review your overall health and hospital course. These assessments will occur while you are in the hospital. You will not be kept in the hospital any longer than your treating doctors think is medically necessary.
At approximately 1 month after the study treatment, our site study team may call you or your representative to ask about any medications you may be taking and your current health status if the study team cannot find this information in your medical records.

Our site team and the study team from Vanderbilt University will need contact information for multiple contacts to help ensure that their efforts to contact you will be successful. The study team will request contact information (such as cell number, home number, work number, address, email) from you and additional contacts of your choosing. Any contact information you or your family choose to share with us will remain confidential and will be stored in a password protected database.

There are no outpatient (clinic) appointments associated with this study.

At approximately 3 and 6 months after end of study treatment, study team members from Vanderbilt University will call or videocall you to ask about your ability to think clearly, quality of life, mobility, and function, and what you remember from your time in the ICU. This phone/ video call should take about 1 hour.

What are the potential benefits of participating in this study?

You may or may not benefit as a result of your participation in this study. With either study treatment, additional close monitoring from the study team may help ensure sedation is carefully adjusted to within the range prescribed by the treating physician. Isoflurane may decrease the need for opioids (pain medications) while on the ventilator. Participants receiving isoflurane may wake up faster once sedation is stopped. Results from this study may benefit others in the future and help us identify best options for sedation in patients on the ventilator in the ICU.

What are the risks or side effects of participating in this study?

All treatments have risks and may cause side effects. These may happen to you from the study treatment. These effects could be mild or serious. In some cases, these effects might be long lasting or permanent, and might be life-threatening. It is possible some risks may not be known at this time.

The study medications will only be given while you are in the ICU and on continuous monitoring, and you will be closely observed for side effects throughout the study. The study doctor or study staff may give you treatment to help reduce any side effects or stop the study treatment early. The side effects that are most likely to happen to you if you take part in this study are noted below.

Risks of Propofol given Intravenously:

Propofol has been shown to be safe and effective for ICU sedation in well controlled clinical trials and was approved for the sedation of ICU patients on the ventilator in 1993. Propofol for ICU sedation is considered part of the standard of care in the United States and around the world. The dose and administration of propofol used in this study follows FDA-approved dosing instructions.

Common side effects of propofol (which occur in more than 1 in 10 patients) include a decrease in blood pressure, heart rate, or breathing effort. Discomfort, itching, or a rash at the IV site may occur occasionally.

Rare but potentially serious side effects of propofol (which occur in far less than 1 in 100 patients) include:

- Allergic reactions
- Abnormal heart rhythm
- Pancreatitis (inflammation of the pancreas, which can cause pain and nausea)
- Propofol infusion syndrome: a rare but life-threatening condition characterized by too much acid in the blood, high potassium, muscle breakdown, and/or heart, kidney, and liver failure. This rare event is most commonly reported at higher doses and longer durations than will be used in this study.

Risks of Isoflurane given Inhaled with the Sedaconda ACD-S:

Isoflurane has been shown to be safe and effective for deep sedation (anesthesia) during surgery and is routinely used for that purpose in the United States and around the world. Isoflurane administered via the Sedaconda ACD-S is approved for sedation of ventilator-dependent ICU patients in Europe but not yet in the United States. The dose of isoflurane administered for ICU sedation is generally lower than required during surgery, and so dose-dependent side effects may be less common and less severe.

Common side effects of isoflurane (which occur in more than 1 in 10 patients) include a decrease in blood pressure, heart rate, or breathing effort. Nausea may occur occasionally.

Rare but potentially serious side effects of isoflurane (which occur in far less than 1 in 100 patients) include:

- Allergic reactions
- Abnormal heart rhythm
- Increased liver enzymes which may be a sign of liver dysfunction

Very rare but potentially serious side effect of isoflurane (which occurs in far less than 1 in 10,000 patients) include:

- Malignant hyperthermia (high body temperature, rigid muscles, rapid heart rate)

One event of further increased pressure in the brain was observed in an adult participant with elevated pressure in the brain being treated with Sedaconda/Isoflurane.

Preliminary results from a Sedaconda/Isoflurane study in children identified one participant who developed confusion, one participant who had lower blood pressure, and one participant with increased pressure in the brain who had further increased pressure in the brain.

Common side effects of using the Sedaconda ACD-S device include a slight increase in the amount of carbon dioxide in the blood. Rare potential side effects of the Sedaconda ACD-S include a decrease in the amount of sedation received over time or increase in breathing circuit resistance if the device becomes clogged by moisture or sputum.

Risks from Other Study Procedures:

- **Blood Samples:** Possible adverse effects from drawing blood include faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection.
- **Video/ Telephone Assessments**: The follow-up telephone assessments of your thinking, quality of life, and physical function could be emotionally uncomfortable. If this occurs, you may choose to end the phone/video call at any time and are not required to answer any questions you do not want to answer.

Other Unknown Risks:

Since the use of Isoflurane administered via the Sedaconda ACD-S is an investigational study treatment, there may be other risks that are unknown. All medications have the potential risk of an allergic reaction, which if not treated promptly, could become life-threatening. Symptoms of an allergic reaction could be trouble breathing, or swelling of the face, mouth, lips, gums, tongue, or neck. Other symptoms of an allergic reaction may include rash, hives, or blisters. In the event of an allergic reaction, you will be treated promptly by the staff in the ICU. You will not be allowed to participate if you have a known allergy to propofol or if you or a family member has had a severe reaction to anesthesia (such as malignant hyperthermia).

It is important that you tell the study doctor about any adverse changes in your health as soon as they occur, whether or not you think they are caused by the study treatment.

Risk of Loss of Privacy:

Every reasonable step will be taken to protect your privacy and confidentiality. Participation in any research study, including this one, may involve a risk of loss of privacy, and absolute confidentiality cannot be guaranteed. To minimize this risk, we will assign codes instead of using names and personal information. All information collected on paper will be kept in a secure location. Information collected on computer will be password protected and stored on a secure network. Staff at the study site will handle your personal information very carefully. We are required to make sure that people not involved with the study do not have access to your records. When results of the research are published or discussed at conferences, no information will be included that would reveal your identity.

Birth Control and Pregnancy-related Risks?

The effect of the study treatment in an unborn baby, a breast fed child, the female egg or on sperm is unknown. Therefore, you cannot participate in this study if you are pregnant or breast-feeding. If you are found to be pregnant during the 7 day follow-up after end of study treatment, the study staff will collect information about the pregnancy, its outcome, and the health of the child after birth.

What happens if there is new information?

Sometimes during the course of a research study, new information becomes available about the study treatment. The study doctor will inform you in a timely manner about any new important

information that is discovered while you are in the study and discuss with you if you want to continue in the study. If this occurs, you may be asked to sign and date an updated consent form to confirm you agree to continue in the research study.

The study doctor may remove you from the study at any time without your consent if:

- Your study doctor does not consider it to be in your best interest to continue.
- Your study doctor has received new information about the safety or effectiveness of the study treatment that would cause you to no longer be able to participate.
- You cannot tolerate the study treatment.
- The study is stopped by the study site, the Sponsor, or regulatory authorities
- For administrative reasons

What happens if you are injured during the study?

If you are hurt or suffer other physical injury as a direct result of taking part in the study, the Sponsor will pay for the reasonable costs of medical treatment in accordance with applicable laws. The study site will treat your injury right away. The Sponsor has insurance to cover such costs, and will make these payments where the adverse effect or other physical injury resulted from:

- A medicine being tested or administered as part of the study, or
- Any test or procedure you received as part of the study.

The Sponsor will only pay for the medical costs that are not covered by your insurance or other programs. If you have medical insurance, check with your insurance company that taking part in this study will not affect your policy. There are no plans for the Sponsor to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for the Sponsor or study site to give you money for the injury. By signing and dating this document, you will not lose any of your legal rights or release anyone involved in the research from responsibility for mistakes.

What are the costs to you of taking part in the study?

There are no costs for you if you take part in this study. You will receive the study treatment at no charge, and you will not be charged for any study-related procedures. You are still responsible for paying for the usual care you would normally receive for the treatment of your illness. You, your insurance company, or some other third-party payer must pay for all other medicines and hospital costs.

Will you be paid to be in this study?

If you are enrolled and randomized into the study, you will receive a $50.00 check for completing the 3-month follow-up phone assessment and a $50.00 check for completing the 6-month follow-up phone assessment. Vanderbilt University is responsible for providing these payments to you. Your reimbursement checks should arrive in about 6-8 weeks after each follow up phone/video call. We may use your Social Security Number, name, and address in order to process your compensation for taking part in this study.

How will your privacy be protected?

Confidentiality

Once this consent form is signed and dated, you will be assigned a study code. During the study, the study doctor and study staff will collect information about you, including demographics, health data, and results of study procedures. Your records and study data (information) will not include

your name or personal identity but will identify you with a study code. This code can only be tracked back to you via a code key that is held by authorized study personnel at the site. Although procedures are in place to protect your privacy, absolute confidentiality cannot be guaranteed.

Authorization to Use and Disclose Protected Health Information

Access to your health information is required for this study. If you choose to take part in this study, you are giving us permission to use the protected health information and information collected during research that can identify you. The health information that we may collect and use for this research includes your past, present, and future physical or mental health and condition, and results of lab tests, examinations, or procedures. Information needed for this research may be obtained from any hospital, doctor, or other healthcare provider involved in your care. The research information that is shared with people outside of [site/hospital name], with the exception of research team members from Vanderbilt University who will be performing the follow-up phone/video calls, will not include your name, address, telephone number, or other direct identifiers unless disclosure of the information is required by law, or you have authorized the disclosure. Study personnel are required by law to protect your health information.

By signing and dating this document, you authorize [site/hospital name] to use and/or disclose (release) your health information for this research. Those who receive your health information may not be required by federal privacy laws to protect it and may share your information with others without your permission, if allowed by laws governing them. Your authorization to use and share your health information does not have an expiration (ending) date. You may change your mind and revoke (take back) this consent and authorization at any time and for any reason. To revoke this consent and authorization, you must contact the study physician identified on the first page of this document. If you revoke your consent and authorization, you will not be allowed to continue taking part in the research. Also, even if you revoke this consent and authorization, the Researchers and the Sponsor may continue to use and disclose the information they have already collected.

Data will be stored, processed, and compiled by the Sponsor both manually and electronically. Your collected information will be used and disclosed only in accordance with the law. Your identity will not be shared in any reports or publications resulting from this study. Your information will be identified only by your study code when sent to the Sponsor. Your study information may be disclosed to and used by:

- The study doctor and study staff
- The Critical Illness, Brain Dysfunction, and Survivorship Center at Vanderbilt University, who will be conducting the follow-up phone/video calls
- Sedana Medical AB, the study Sponsor paying for this research study
- Medpace, the contract research organization facilitating the study on behalf of Sponsor
- Authorized representatives and contractors of the Sponsor or Medpace
- U.S. Food and Drug Administration (FDA)
- Other agencies in the U.S. and other countries that have the authority to review study records
- Ethics committees overseeing the study, including Advarra Institutional Review Board (IRB)
- Any successors to any of these organizations.

They are committed to protecting your privacy. As the research staff at the study site, we are required to make sure that people not involved with this study cannot see your research and

medical information. We will keep your research files in a safe place and will handle your personal information very carefully.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can you contact about this study?

If you have any questions or concerns about the research or your rights as a participant, an injury, or are unwell, please contact the study doctor at the telephone number listed on the first page of this document.

All research studies are reviewed by an independent group of people called the IRB to help protect the rights of research participants. This study has been reviewed and approved by the IRB. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, you should write to [IRB name and address], or call [IRB phone number].

STATEMENT OF CONSENT AND HIPAA AUTHORIZATION TO PARTICIPATE IN THE INSPIRE STUDY

I have read or had explained to me the information in this consent form. I believe that I understand this information. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. By signing and dating this consent, I am stating that I want to join this study and authorize the use and disclosure of my health information to conduct this study. I do not give up any of my legal rights by signing this consent form. I will receive a copy of this signed and dated consent form.

_____	_____	_____
Research Participant: Print Name	*Research Participant: Signature*	*Date & Time*

– OR –

[ ] Study participant lacks capacity to consent. Consent given by LAR below.

LEGALLY AUTHORIZED REPRESENTATIVE

If consent was provided by a legally authorized representative (LAR), complete below.

You are being asked as the legally authorized representative (LAR) to permit the participant to take part in the research. By signing below, you indicate you agree that the person named above can take part in this study.

_____	_____
LAR: Print Name	*LAR Relationship to Participant*

_____ _____

LAR: Signature *Date & Time*

STUDY STAFF OBTAINING CONSENT

_____ _____ _____

Study Staff: Print Name *Study Staff: Signature* *Date & Time*

WITNESS SIGNATURE FOR PARTICIPANTS WHO CANNOT READ

The study participant has indicated that he/she is unable to read. The consent document has been read to the participant by study staff, discussed with the participant by study staff, and the participant has been given an opportunity to ask questions of the study staff.

_____ _____ _____

Impartial Witness: *Print Name Impartial Witness: Signature* *Date & Time*