Appendix D

1.0. Definition of Adverse events

- Hypoxemia: Minor hypoxemic event will be defined sustained hypoxemia within 90 minutes of FiO2 titration of Spo2 less than 88% for greater than 15 minutes, resolved with increase in FiO2 and or one time increase in PEEP.
- Hypoxemia: Major hypoxemic event will be defined a sustained hypoxemia within 90 minutes of FiO2 titration of Spo2 less than 88% for greater than 15 minutes, requiring changes in multiple ventilator parameters, discontinuation from the ventilator and bag valve mask use or ventilator/ non- ventilator strategies for management of refractory hypoxemia.
- New onset arrhythmia after enrollment in the study associated with hypoxemia
- New onset shock after enrollment in the study (defined as lactate greater than 4, with new and escalating vasopressor use)
- Death in hospital

1.1. Serious adverse event collection begins after randomization and study procedures have been initiated. If a patient experiences a serious adverse event prior to starting study procedures, the event will NOT be collected. Study coordinator will report study procedure related adverse event within 24 hours of investigator awareness of the event. The medical monitor will make the determination of a serious adverse event.

As per the FDA and NIH definitions, a serious adverse event is any adverse event that results in one of the following outcomes:

- Death
- A life-threatening experience (that is, immediate risk of dying)
- Prolonged inpatient hospitalization or re-hospitalization

Based on the above, we would consider the following among the above as SAE:

- Major hypoxemic event: Sustained hypoxemia (SpO2 less than 88% for greater than 15 minutes) requiring changes in multiple ventilator parameters, discontinuation from the ventilator and Ambu bag use or ventilator/ non- ventilator strategies for management of refractory hypoxemia
- New onset arrhythmia after enrollment in the study associated with hypoxemia (only if associated with hemodynamic compromise)
- New onset shock after enrollment in the study (defined as lactate > 4, with new and escalating vasopressor use)
- Death in hospital

1.2. Serious adverse events will be collected until hospital discharge or first 30 days, whichever occurs first, regardless of the investigator's opinion of causation.

1.3. Determining Relationship of Adverse Events to Study Procedures: The Medical Monitor will work collaboratively with the study coordinator to determine if a serious adverse event has a reasonable possibility of having been caused by the study procedure. He will be asked to grade the strength of the relationship of an adverse event to study drug or study procedures as follows:

Definitely Related: The event follows: a) A reasonable, temporal sequence from a study procedure; and b) Cannot be explained by the known characteristics of the patient's clinical state or other therapies; and c) Evaluation of the patient's clinical state indicates to the monitor that the experience is definitely related to study procedures.

Probably or Possibly Related: The event should be assessed following the same criteria for "Definitely Associated". If in the investigator's opinion at least one or more of the criteria are not present, then "probably" or "possibly" associated should be selected.

Probably Not Related: The 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 event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.

Uncertain Relationship: The event does not meet any of the criteria previously outlined.

1.4. Unanticipated problems: Study coordinators will report Unanticipated Problems, regardless of severity, associated with study procedures within 24 hours to the investigator. These events will be noted and reported to the DSMB.

An unanticipated problem is defined as follows: any incident, experience, or outcome that meets all of the following criteria:

- Unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and the characteristics of the subject population being studied;
- Related or possibly related to participation in the research, in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research;
- 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.

The study is monitored by a Data and Safety Monitoring Board and an independent medical monitor has also been appointed.

Data and Safety Monitoring Board is overseeing the study. The DSMB is established to ensure participant safety, ensure the validity and integrity of the data, monitor study progress, and make recommendations regarding appropriate protocol and operational changes which may have substantial effects upon the ultimate interpretation of the study. The DSMB is comprised of experienced members with expertise in either the scientific field of study, clinical trials, statistics, research ethics and/or epidemiology three scientists who are independent of the study investigators. The DSMB reviews protocol - specific reports created by the research team. These standard reports include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of patient demographics for balance of randomization, weekly adherence data and a summary of the type, frequency, attribution, severity, seriousness and expectedness of adverse events. The study coordinator has access to aggregated and unblinded data. The study coordinator will send De-identified data to the study statistician for analysis. If the DSMB needs to see unblinded data- they will be provided extracted data from the study coordinator. If needed by the DSMB, the statistician can be unblinded. Accruals, withdrawals, and protocol violations of enrollment will be reported at the DSMB meetings. DSMB will make recommendations to the Principal Investigator that could include actions of continuation, modification, suspension, or termination.

In providing oversight for the conduct of this study, the DSMB will meet at a minimum of every 6 months during the 18-month study to review all salient study information. Additional meetings may be scheduled as determined by the DSMB. All serious adverse events regardless of severity, attribution and/or expectedness will be reported to the DSMB and the Ohio State University IRB oversight committee in accordance with their reporting guidelines. The DSMB recommended actions and all pertinent regulatory information will be forwarded to the appropriate Institutional Review Board(s).

A medical monitor is appointed for this study. He is not a member of the study team. He is responsible for real-time monitoring of reports of serious adverse events submitted by the research personal to identify safety concerns quickly and to provide the Data Safety Monitoring Board with case-by-case reports of the serious adverse events. The medical monitor is blinded and makes determinations of severity and relatedness.

Guidelines to the Medical Monitor for grading adverse events

Adverse events	**Definition**	**Action taken to resolve**	**Grade**
Minor hypoxemic event	Sustained hypoxemia within 90 minutes of FiO2 titration of Spo2 less than 88% for greater than 15	Increase in FiO2 by 0.1	MILD
		Increase in FiO2 by 0.2	MILD

	minutes, resolved with increase in FiO2 and or one time increase in PEEP	Increase in FiO2 0.1 or 0.2 and any increase in PEEP	MODERATE
		Increase in FiO2 >0.2 and any one time increase in PEEP <=2 cms.	SEVERE
Major hypoxemic event	Sustained hypoxemia within 90 minutes of FiO2 titration of Spo2 less than 88% for greater than 15 minutes, requiring changes in multiple ventilator parameters, discontinuation from the ventilator and bag valve mask use or ventilator/ non-ventilator strategies for management of refractory hypoxemia	Increase in FiO2 >0.2 and any one time increase in PEEP > 2cms	MILD
		Increase in FiO2 >0.2 and any one time increase in PEEP > 2cms combined with any other vent parameter changes- Change in I:E ratio, peak flow, recruitment maneuver; change in ventilator mode (PRVC/ AC/PC/ bi-level)	MODERATE
		Any of the above changes along with discontinuation of the ventilator, oxygenation with bag, mask valve ventilation	MODERATE
		Any of the above events, and need for prone position; inhaled vasodilator or Extra corporeal oxygenation	SEVERE
New onset arrhythmia	New onset arrhythmia after enrollment in the study associated with hypoxemia	Resolved with increase in FiO2	MILD
		New onset arrhythmia (not resolved with increase in FiO2 or	MODERATE

		less than 2 cm change in PEEP) causing worsening hypoxemia	
		New onset arrhythmia with hemodynamic compromise	SEVERE
New onset shock	New onset shock associated with hypoxemia (Spo2 less than 88% for atleast 15 mins or PaO2 less than 60) after enrollment in the study (defined as lactate greater than 4, with new and escalating vasopressor use)	New onset shock improving by increasing FiO2 or other MV measures	MILD
		New onset shock responding to increased FiO2 or other MV measures and fluids (in addition to initial vasopressor use)	MODERATE
		New onset shock not resolving by any of the above, needing third line vaso-pressors	SEVERE