Strategies For Anticoagulation During Venovenous ECMO: The SAFE-ECMO Pilot Trial

Title	**Strategies For Anticoagulation During Venovenous ECMO: The SAFE-ECMO Pilot Trial**
Acronym	
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Clinical Trial Protocol

Trial Summary

Title: Strategies For Anticoagulation During Venovenous ECMO: The SAFE-ECMO Pilot Trial

Background: Since the inception of extracorporeal membrane oxygenation (ECMO), moderate intensity titrated dose anticoagulation has been used to prevent thromboembolism and thrombotic mechanical complications. As technology has improved, however, the incidence of thromboembolic events has decreased, leading to re-evaluation of the risks of anticoagulation, particularly during venovenous (V-V) ECMO. Recent data suggest that bleeding complications during V-V ECMO may be more strongly associated with mortality than thromboembolic complications, and case series have suggested that V-V ECMO can be safely performed without moderate or high intensity anticoagulation. At present, there is significant variability between institutions in the approach to anticoagulation during V-V ECMO. A definitive randomized controlled trial is needed to compare the effects of a low intensity fixed dose anticoagulation (low intensity) versus moderate intensity titrated dose anticoagulation (moderate intensity) on clinical outcomes during V-V ECMO. Before such a trial can be conducted, however, additional data are needed to inform the feasibility of the future trial.

Primary aim: To demonstrate feasibility of a future large, multi-center randomized controlled trial comparing low intensity to moderate intensity anticoagulation among adults receiving V-V ECMO by demonstrating the ability to recruit and randomize participants, adhere to assigned anticoagulation strategy, and demonstrate adequate separation between groups in therapy delivered and intensity of anticoagulation achieved with the assigned anticoagulation strategies.

Secondary aim: To define and estimate the frequency of the primary efficacy, primary safety, and secondary outcomes of a future large, multi-center randomized controlled trial comparing low intensity vs moderate intensity anticoagulation among adults receiving V-V ECMO.

Inclusion criteria:

1. Patient receiving V-V ECMO
2. Patient is located in a participating unit of an adult hospital

Exclusion criteria:

1. Patient is pregnant
2. Patient is a prisoner
3. Patient is < 18 years old
4. Patient underwent ECMO cannulation greater than 24 hours prior to screening
5. Presence of an indication for systemic anticoagulation:
    a. Ongoing receipt of systemic anticoagulation
    b. Planned administration of anticoagulation for an indication other than ECMO
    c. Presence of or plan to insert an arterial ECMO cannula
6. Presence of a contraindication to anticoagulation:
    a. Active bleeding determined by treating clinicians to make anticoagulation unsafe
    b. Major surgery or trauma less than 72 hours prior to randomization
    c. Known history of a bleeding diathesis
    d. Ongoing severe thrombocytopenia (platelet count < 30,000)
    e. History of heparin induced thrombocytopenia (HIT)
    f. Heparin allergy

7. The treating clinician determines that the patient's risks of thromboembolism or bleeding necessitate a specific approach to anticoagulation management during V-V ECMO

Consent: Patients or their surrogates will provide written informed consent to study personnel.

Randomization: After enrollment, patients will be randomized in a 1:1 ratio to initiation of either low intensity anticoagulation or moderate intensity anticoagulation. The randomization will be performed electronically through REDCap using permuted randomized blocks of two, four, and six.

Study interventions:

- **Low intensity anticoagulation**: For patients assigned to the low intensity anticoagulation strategy, clinical teams will be instructed to initiate low intensity anticoagulation at doses and frequencies commonly used for deep vein thrombosis (DVT) prophylaxis. The choice of anticoagulant, dose, and frequency of administration will be deferred to treating clinicians.
- **Moderate intensity anticoagulation**: For patients assigned to the moderate intensity anticoagulation group, clinical teams will be instructed to initiate a continuous infusion of moderate intensity anticoagulation targeting either a partial thromboplastin time (PTT) of 40-60 seconds or an Anti-Xa level of 0.2 to 0.3 IU/mL. The choice of anticoagulant and approach to dosing will be deferred to treating clinicians.

Duration of Study Interventions:

- The protocol will control the anticoagulation strategy from randomization until the first of: diagnosis of a major bleeding event, diagnosis of a thromboembolic event, placement of an arterial ECMO cannula, decannulation from ECMO, or death. Treating clinicians may change anticoagulation strategy at any point if determined to be necessary for optimal patient care.

Primary efficacy outcome:

- Major bleeding, according to the International Society on Thrombosis and Hemostasis definition[1], from randomization to 24 hours after decannulation defined as:
    a. Fatal bleeding
    b. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome
    c. Clinically overt bleeding associated with either a drop in hemoglobin level by at least 2.0 grams/dL or leading to transfusion of two or more units of packed red blood cells

Primary safety outcome:

- Thromboembolic event from randomization to 24 hours after decannulation, defined as:
    a. Deep venous thrombosis (DVT)
    b. Acute pulmonary embolism (PE)
    c. Intra-cardiac thrombosis
    d. Ischemic stroke
    e. Acute circuit thrombosis requiring urgent circuit exchange
    f. Acute arterial thromboembolism

Feasibility outcomes:

- Number of patients screened per month
- Number of patients who are eligible per month
- The specific exclusion criteria met (for any patient ineligible for enrollment)
- Reasons for "missed" enrollments (e.g. unavailability of research staff, refusal of clinical team to allow randomization, patient refusal of informed consent)
- Number of patients enrolled per month
- Adherence to the assigned anticoagulation strategy
- Separation between groups in anticoagulation treatment received
- Time from ECMO cannulation to randomization
- Duration of the intervention period, defined as the time from randomization to the first of: diagnosis of a major bleeding event, diagnosis of a thromboembolic event, placement of an arterial ECMO cannula, decannulation from ECMO, or death

Secondary outcomes:

- Cannula-associated DVT, as measured by four-extremity venous ultrasounds obtained 24-72 hours following decannulation
- Bleeding events per ECMO day
- Thromboembolic events per ECMO day
- Bleeding events from randomization to the first of death or discharge
- Thromboembolic events from randomization to the first of death or discharge
- Circuit or circuit component exchange required during ECMO support
- ECMO circuit durability, calculated as the number of calendar days from randomization to death or decannulation divided by the number of ECMO circuits used
- RBC transfusion volume per ECMO day, calculated as the total volume of packed red blood cells transfused from randomization to death or decannulation divided by the number of calendar days during this period
- New diagnosis of HIT from randomization to the death or decannulation from ECMO, as measured by clinically obtained serotonin release assay
- Lowest documented platelet count from randomization to 24 hours after decannulation
- Highest Total and indirect bilirubin values from randomization to 24 hours after decannulation
- Highest LDH value values from randomization to 24 hours after decannulation
- Death attributable to a major bleeding event
- Death attributable to a thromboembolic event
- Ventilator-free days
- ECMO-free days
- ICU-free days
- Hospital-free days
- In-hospital mortality

1 Background

Since the inception of Extracorporeal Membrane Oxygenation (ECMO), moderate intensity titrated dose anticoagulation has been used to prevent clinically harmful thromboembolism and thrombotic mechanical complications. The impact of thromboembolic events on clinical outcomes during venovenous (V-V) extracorporeal membrane oxygenation (ECMO), however, is unclear, and complications related to bleeding are common and associated with increased morbidity and mortality.[2-7] These findings have led many experts to suggest that anticoagulation strategies during V-V ECMO should be re-evaluated.

Critical illness, in general, is associated with both coagulopathy and impaired hemostasis.[8] These problems are compounded during ECMO by the artificial interface between blood and the non-biologic surface of the circuit components, which leads to activation of the coagulation system, consumptive thrombocytopenia, fibrinolysis, and thrombin generation.[8-10] The sheer stress on blood components during ECMO also lead to destruction of high-molecular-weight von Willebrand multimers, interrupting primary hemostasis.[11]

Both bleeding and thromboembolism are common complications during ECMO.[2-7] Bleeding events have been associated with poor clinical outcomes, likely mediated by an increased incidence of intracranial hemorrhage during ECMO.[2,12] During intra-operative cardiopulmonary bypass and venoarterial (V-A) ECMO, ischemic strokes are a common and potentially deadly complication. During V-V ECMO, however, the majority of thromboembolic events are cannula-associated DVT and circuit thromboses requiring exchange, which are of unclear clinical significance.[13-15]

Various anticoagulation strategies have been proposed to balance the risks of bleeding and thromboembolism during V-V ECMO, including high intensity anticoagulation, moderate intensity anticoagulation, and low intensity anticoagulation (the equivalent of DVT prophylaxis). Observational studies have suggested that, compared to moderate intensity anticoagulation, low intensity anticoagulation reduces transfusion requirements without affecting the incidence of thrombosis, hemorrhage, or death.[16-18] In one case series of 60 patients who were treated with only low-intensity subcutaneous heparin during V-V ECMO, rates of transfusions were lower than historical controls without any effect on the rate of thrombotic events.[16] Similarly, a recent systematic review suggested that the rates of thromboembolism and circuit thrombosis among patients managed with a moderate intensity anticoagulation strategy during V-V ECMO were comparable to the rates reported among patients managed with a less intense anticoagulation strategy.[19]

To date, there are no randomized controlled trials comparing low intensity to moderate intensity anticoagulation during V-V ECMO. Guidelines from the Extracorporeal Life Support Organization (ELSO), the pre-eminent group for ECMO education and research, provide little guidance for the selection of anticoagulation strategy,[20] and anticoagulation practices are highly variable across institutions.[8,21] A large, multicenter, randomized trial is needed to determine the ideal strategy to anticoagulation during V-V ECMO. Before such a trial can be conducted, however, additional data are needed on the feasibility of randomizing patients to a specific anticoagulation strategy and study measurements.

2 Rationale, Aims, and Hypotheses

To facilitate a large, multicenter randomized controlled trial comparing low intensity anticoagulation to moderate intensity anticoagulation during V-V ECMO, a pilot trial is needed to establish feasibility and the performance of the primary outcome measures.

2.1 Study Aims

- **Primary aim:** To demonstrate feasibility of a future large, multi-center randomized controlled trial comparing low intensity to moderate intensity anticoagulation among adults receiving V-V ECMO by demonstrating the ability to recruit and randomize participants, adhere to assigned anticoagulation strategy, and demonstrate adequate separation between groups in therapy delivered and intensity of anticoagulation achieved with the assigned anticoagulation strategies.

- **Secondary aim:** To define and measure the primary efficacy, primary safety, and secondary outcomes of a future large, multi-center randomized controlled trial comparing low intensity vs moderate intensity anticoagulation among adults receiving V-V ECMO.

3 Study Description

To address these aims, we propose a single center, open-label, parallel-group, randomized pilot trial comparing low intensity anticoagulation to moderate intensity anticoagulation among patients receiving V-V ECMO. All patients who receive V-V ECMO in a participating ICU of an adult hospital and meet all inclusion and no exclusion criteria will be eligible for participation. Eligible participants or surrogate decision makers will be approached for consent. Following documentation of written informed consent, patients will be enrolled and randomly assigned to low intensity or moderate intensity anticoagulation. The study will control anticoagulation from randomization until the first of: diagnosis of a major bleeding event, diagnosis of a thromboembolic event, placement of an arterial ECMO cannula, decannulation from ECMO, or death. All other decisions regarding critical care support, interventional therapies, and medical treatment will remain at the discretion of the treating physician and consulting clinical teams.

4 Study Population, Inclusion and Exclusion Criteria

4.1 Study Population

All adult patients receiving V-V ECMO will be screened for eligibility. Patients meeting all inclusion and no exclusion criteria will be approached for consent. To be eligible for enrollment, the patient must meet all inclusion criteria and no exclusion criteria at the time of screening and randomization. Screening and randomization must be accomplished within 24 hours of ECMO cannulation.

4.2 Inclusion Criteria

1. Patient receiving V-V ECMO
2. Patient is located in a participating unit of an adult hospital

4.3 Exclusion Criteria

1. Patient is pregnant
2. Patient is a prisoner
3. Patient is < 18 years old
4. Patient underwent ECMO cannulation greater than 24 hours prior to screening
5. Presence of an indication for systemic anticoagulation:
    a. Ongoing receipt of systemic anticoagulation
    b. Planned administration of anticoagulation for an indication other than ECMO
    c. Presence of or plan to insert an arterial ECMO cannula
6. Presence of a contraindication to anticoagulation:
    a. Active bleeding determined by treating clinicians to make anticoagulation unsafe
    b. Major surgery or trauma less than 72 hours prior to randomization
    c. Known history of a bleeding diathesis
    d. Ongoing severe thrombocytopenia (platelet count < 30,000)
    e. History of heparin induced thrombocytopenia (HIT)
    f. Heparin allergy
7. The treating clinician determines that the patient's risks of thromboembolism or bleeding necessitate a specific approach to anticoagulation management during V-V ECMO

5 Determination of Eligibility, Consent, Enrollment, and Randomization

5.1 Study Sites

1. Participating intensive care units at the VUMC adult hospital.
2. Participating intensive care units at Stanford Medical Center
3. Participating intensive care units at Duke University Medical Center

5.2 Determination of Eligibility

All patients meeting inclusion criteria will be screened for eligibility and assigned a deidentified study identification number. If a patient appears to meet all inclusion criteria and no exclusion criteria, the site investigator or delegate will approach the treating clinician to ask permission to approach the patient or Legally Authorized Representative (LAR) to confirm eligibility, discuss potential study recruitment, and proceed with informed consent.

For all excluded patients, including refusal by the treating clinician or patient/surrogate, a small number of de-identified variables will be collected including month and year the patient met screening criteria, patient location, and reason(s) patient was excluded.

5.3 Process of Obtaining Informed Consent

Written informed consent will be obtained from the patient or from a surrogate decision maker if the patient lacks decision-making capacity. Consent will be obtained by a key study personnel who has undergone good clinical practice (GCP) training and is authorized to obtain written informed consent.

Given that patients are critically ill and frequently receiving invasive mechanical ventilation at the time of cannulation for V-V ECMO, it is expected that consent will be provided from a surrogate decision maker in the majority of cases. Further, decisions regarding anticoagulation must be made shortly after cannulation. ECMO cannulation is an emergent procedure so surrogate decision makers may not be available in-person at the time of screening and consent. Therefore, in addition to the traditional approach of in-person, written informed consent, we will use an electronic/e-consent approach to allow remote consent of surrogate decision makers.

This approach complies with relevant regulations and sub-regulator guidance at 45 CFR 46.117, 45 CFR 164.512, 21 CFR 11 Subpart C (11.100–11.300), https://www.hhs.gov/ohrp/regulations-and-policy/guidance/use-electronic-informed-consent-questions-and-answers/index.html, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent.

The information for the informed consent discussion will be provided in a formal document (or electronic equivalent) that has been approved by the IRB and in a language comprehensible to the potential participant, using an interpreter if necessary. The information presented in the consent form and by the research staff will detail the nature of the trial and what is expected of participants, including any potential risks or benefits of taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

5.4 Enrollment

Patients who meet inclusion criteria but no exclusion criteria and provide written informed consent will be enrolled immediately after written informed consent has been obtained *and* eligibility has been confirmed with the treating physician. Patients who initially meet all inclusion criteria and no exclusion criteria at the time of screening but develop a change in clinical status that prohibits receipt of either study treatment prior to randomization (i.e. development of one or more exclusion criteria or death) will be excluded from study participation and prospectively recorded.

5.5 Randomization and Blinding

Immediately following enrollment patients will be randomized in a 1:1 ratio to either a low intensity or moderate intensity anticoagulation strategy. The randomization will be performed through REDCap using random permuted blocks of two, four, and six, stratified by site. The study group assignment will remain concealed to study personnel and treatment teams until after the decision has been made to enroll the patient in the study and written informed consent has been obtained. Following randomization, the treatment team and ECMO consultant team will be notified of a patient's assigned anticoagulation strategy. Given the nature of the intervention blinding is not feasible.

6 Study Procedures

6.1 Study Interventions

Determination of eligibility, written informed consent, study enrollment, and randomization must be completed within 24 hours of ECMO cannulation in order for a patient to be included in the

study. Prior to randomization, the anticoagulation management strategy will be left to the discretion of the treatment team.

Following randomization, the study controls maintenance anticoagulation strategy until the first of: diagnosis of a major bleeding event, diagnosis of a thrombotic event, placement of an arterial ECMO cannula, decannulation from ECMO, or death.

The study does not control anticoagulation for procedural indications (e.g. during ECMO cannulation or cardiac catheterization), and it does not control the use of anti-platelet agents (e.g. aspirin or clopidogrel).

6.1.1 Low Intensity Anticoagulation Group

Participants assigned to the low intensity anticoagulation strategy will receive anticoagulation at doses used for DVT prophylaxis in critically ill patients. The choice of agent (e.g. heparin or enoxaparin) and specific dosing will be at the discretion of the treating clinicians and will be prospectively recorded.

This strategy of anticoagulation is intended to expose the patient to less systemic anticoagulation and was chosen to balance the risks of bleeding and thromboembolism during V-V ECMO. While most available guidelines recommend moderate intensity anticoagulation during V-V ECMO for patients without contraindications, it has been noted that bleeding events are common and frequently associated with poor clinical outcomes. Further, patients with contraindications to anticoagulation (e.g. recent surgery or trauma) are frequently managed without any anticoagulation during V-V ECMO and studies have suggested that the incidence of thromboembolism and circuit thrombosis among these patients is similar to that observed among patients receiving moderate intensity anticoagulation.

6.1.2 Moderate Intensity Anticoagulation Group

Patients assigned to the moderate intensity anticoagulation strategy will receive anticoagulation targeting a PTT goal of 40-60 seconds or anti-Xa level of 0.2 to 0.3 IU/mL.

Choice of anticoagulant and monitoring strategy (PTT or anti-Xa level) will be at the discretion of the treating clinicians and will be prospectively recorded. Anticoagulant drips will be titrated according to institutional protocols. For patients who survive to decannulation, the infusion will be stopped one hour prior to decannulation.

This approach to anticoagulation reflects the current approach for patients receiving V-V ECMO at Vanderbilt University Medical Center. While there is significant variation in practice regarding anticoagulation management across ECMO centers[15,22], this protocol is similar to protocols widely adopted for patients receiving V-V ECMO at other centers.[20]

6.1.3 Criteria for Changing Anticoagulation Strategy

The intent of the study is to control maintenance anticoagulation strategy for patients receiving V-V ECMO without a clear indication for, or contraindication to anticoagulation because the relative risks and benefits of low intensity vs. moderate intensity anticoagulation remain unclear in these patients.

If a study participant experiences a major bleeding event, a thromboembolic event (e.g. DVT, PE, stroke, or acute circuit thrombosis), or an arterial ECMO cannula is inserted (which increases the risk of a clinically meaningful thromboembolic event) the study will cease to control anticoagulation strategy and all further decisions regarding anticoagulation will be at the discretion of the clinical team.

There are other conditions that occur commonly in the course of critical illness that may prompt the clinical team to change anticoagulation strategy. If the patient develops any of the following conditions, the protocol will allow the clinical team to change anticoagulation strategy if felt to be in the best interest of the patient, but the protocol will not mandate termination of the assigned anticoagulation strategy:

- Atrial fibrillation
- Acute coronary syndrome
- Thrombocytopenia
- Hemolysis
- Suspected bleeding
- Suspected thromboembolism
- Clinically apparent bleeding not meeting the definition for major bleeding
- Planned procedure
- Lack of parenteral access
- Coagulopathy (elevated INR)
- Suspected or confirmed heparin-induced thrombocytopenia
- Recurrent oxygenator failure
- Anticoagulation given to support continuous renal replacement therapy
    - There are no data to suggest that anticoagulation is superior to a Citrate infusion or no intervention to improve patency of the continuous renal replacement therapy circuit. If the treatment team chooses to intervene to improve continuous renal replacement therapy patency, they will be encouraged to preferentially select a Citrate infusion. Ultimately, the decision will be at the discretion of the treatment team and if anticoagulation is selected to support continuous renal replacement therapy, this will be recorded.
- Visible clot within the ECMO circuit
- Elevated transmembrane pressure or other circuit parameter concerns
- Low ECMO blood flow

At any point during the study, the clinical team will have the ability to change the anticoagulation strategy and use whatever strategy is needed for patient safety.

6.2 Post-Decannulation Surveillance and Anticoagulation Management

Following decannulation, anticoagulation management will be left to the discretion of the treating physician. At 24 to 72 hours post-decannulation, all participants will undergo routine, four-extremity venous ultrasonography for cannula-associated DVT surveillance, in concordance with the current practice for cannula-associated DVT surveillance at Vanderbilt University Medical Center. The exact timing of surveillance and the treatment of any identified DVT will be left to the discretion of the treating physician based on the perceived risks of bleeding relative to benefits of anticoagulation treatment. The presence of any DVT identified by routine surveillance following decannulation will be prospectively recorded.

7 Data Collection and Outcome Measures

7.1 Data Collection

Data will be collected non-invasively as a part of usual care. No additional data will be obtained beyond that which is obtained by bedside observation and from the electronic medical record. The intervention is defined as the time from randomization until the first of: diagnosis of a major bleeding event, diagnosis of a thrombotic event, placement of an arterial ECMO cannula, decannulation from ECMO, or death.

The following variables will be recorded:

Baseline Variable Collection:

- Date and time of hospital admission
- Date and time of ICU admission
- Date and time of intubation (if applicable)
- Age
- Assigned gender at birth
- Height
- Weight
- Body mass index
- Self-reported race
- SAPS II score
- Physiologic parameters at randomization (e.g. heart rate, blood pressure, respiratory rate), receipt of vasopressors (agent, dose)
- Measures of mental status and delirium at randomization [e.g. Richmond Agitation-Sedation Score (RASS), Confusion Assessment Method for the ICU (CAM-ICU), Glasgow Coma Scale (GCS)]
- Indication for ECMO
- Respiratory support immediately prior to ECMO cannulation (e.g. nasal cannula, high flow nasal cannula, non-invasive ventilation, or invasive ventilation)
- Fraction of inspired oxygen immediately prior to ECMO cannulation
- Positive end-expiratory pressure immediately prior to ECMO cannulation
- History of chronic lung disease
- History of lung transplantation
- History of thromboembolism
- History of stroke
- History of major bleeding event
- Chronic receipt of anticoagulation
- Receipt of anticoagulation at the time of randomization (e.g. aspirin, clopidogrel, warfarin, direct-acting oral anticoagulants) in the 7 days prior to randomization
- Active medical problems at randomization (e.g. sepsis, septic shock, acute renal failure requiring renal replacement therapy)
- Most recent complete blood count, creatinine, PTT, Anti-Xa, and INR values prior to randomization

- Most recent arterial blood prior to ECMO cannulation
- Date and time of ECMO cannulation
- ECMO configuration at randomization
- Number and location of ECMO cannula sites at randomization
- Manufacturer and model of ECMO circuit at randomization
- Manufacturer and model of oxygenator at randomization
- ECMO settings at randomization (blood flow, revolutions per minute, sweep gas flow, fraction of delivered oxygen)

Assessments between Randomization and Hospital Discharge

- Date and time of all major bleeding events from randomization to hospital discharge
- Date and time of all thromboembolic events from randomization to hospital discharge
- Anticoagulation strategy at 7 AM each day from randomization to the first of: diagnosis of a major bleeding event, diagnosis of a thrombotic event, placement of an arterial ECMO cannula, decannulation from ECMO, or death; indication for receiving anticoagulation strategy other than intervention strategy
- Randomized assignment to low intensity or moderate intensity anticoagulation strategy
- Number of hours during the intervention period receiving moderate intensity anticoagulation
- Number of hours during the intervention period receiving low intensity anticoagulation
- Date, time, and value of all PTTs and all Anti-XA laboratory results from randomization to 24 hours following decannulation
- Date, time, and type of all major bleeding events from randomization to hospital discharge
- Date, time, and type of all thromboembolic events from randomization hospital discharge
- ECMO blood flow rate, daily during the intervention period
- ECMO fraction of delivered oxygen, daily during the intervention period
- Transmembrane pressures, daily during the intervention period
- Receipt of continuous renal replacement therapy, daily during the intervention period
- Receipt of anticoagulation for continuous renal replacement therapy patency (drug, dose, route of administration), assessed daily during the intervention period
- Volume of packed red blood cells transfused from randomization to 24 hours following decannulation
- Volume of platelets transfused from randomization to 24 hours following decannulation
- Volume of fresh frozen plasma transfused from randomization to 24 hours following decannulation
- Volume of cryoprecipitate transfused from randomization to 24 hours following decannulation
- Lowest documented ECMO blood flow rate during the intervention period
- Date and time of each circuit exchange
- Date and time of each circuit component exchange
- Indication for circuit and circuit component exchanges
- Post-decannulation DVT
- Lowest hemoglobin from randomization to 24 after decannulation
- Lowest documented platelet count from randomization to 24 hours after decannulation
- Highest total and indirect bilirubin values from randomization to 24 hours after decannulation
- Highest LDH value values from randomization to 24 hours after decannulation

- Renal failure requiring renal replacement therapy from randomization to 24 hours after decannulation
- Heparin-induced thrombocytopenia diagnosed by positive serotonin release assay test
- Date and time of decannulation
- Date and time of extubation
- Date of ICU discharge
- Date of hospital discharge
- Date and time of death
- Date and time of arterial cannula placement
- Bleeding event as the primary cause of death
- Thromboembolic event as the primary cause of death

7.2 Outcome Measures

7.2.1 Primary Efficacy Outcome

- Major bleeding, according to the International Society on Thrombosis and Hemostasis definition[1], from randomization to 24 hours after decannulation
    a. Fatal bleeding
    b. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome
    c. Clinically overt bleeding associated with either a drop in hemoglobin level by at least 2.0 grams/dL or leading to transfusion of two or more units of packed red blood cells

7.2.2 Primary Safety Outcome

- Thromboembolic event from randomization to 24 hours after decannulation, defined as:
    a. Deep venous thrombosis (DVT)
    b. Acute pulmonary embolism (PE)
    c. Intra-cardiac thrombosis
    d. Ischemic stroke
    e. Acute circuit thrombosis requiring urgent circuit exchange
    f. Acute arterial thromboembolism

7.2.3 Feasibility Outcomes

- Number of patients screened per month
- Number of patients who are eligible per month
- The specific exclusion criteria met (for any patient ineligible for enrollment)
- Reasons for “missed” enrollments (e.g. unavailability of research staff, refusal of clinical team to allow randomization, patient refusal of informed consent)
- Number of patients enrolled per month
- Adherence to the assigned anticoagulation strategy
- Separation between groups in anticoagulation treatment received
- Time from ECMO cannulation to randomization

- Duration of the intervention period, defined as the time from randomization to the first of: diagnosis of a major bleeding event, diagnosis of a thromboembolic event, placement of an arterial ECMO cannula, decannulation from ECMO, or death

7.2.4 Secondary Outcomes

- Cannula-associated DVT, as measured by four-extremity venous ultrasounds obtained 24-72 hours following decannulation
- Bleeding events per ECMO day
- Thromboembolic events per ECMO day
- Bleeding events from randomization to the first of death or discharge
- Thromboembolic events from randomization to the first of death or discharge
- Circuit or circuit component exchange required during ECMO support
- ECMO circuit durability, calculated as the number of calendar days from randomization to death or decannulation divided by the number of ECMO circuits used
- RBC transfusion volume per ECMO day, calculated as the total volume of packed red blood cells transfused from randomization to death or decannulation divided by the number of calendar days during this period
- New diagnosis of HIT from randomization to the death or decannulation from ECMO, as measured by clinically obtained serotonin release assay
- Lowest documented platelet count from randomization to 24 hours after decannulation
- Highest Total and indirect bilirubin values from randomization to 24 hours after decannulation
- Highest LDH value values from randomization to 24 hours after decannulation
- Death attributable to a major bleeding event
- Death attributable to a thromboembolic event
- Ventilator-free days
- ECMO-free days
- ICU-free days
- Hospital-free days
- In-hospital mortality

8 Data Quality Monitoring and Storage

8.1 Data Quality Monitoring

Data quality will be reviewed remotely using front-end range and logic checks at the time of data entry and back-end monitoring of data using a secure web platform for building and managing online databases (REDCap) to generate data reports. We will perform routine monitoring to examine the completeness and accuracy of informed consent documents for study participants, documentation of eligibility criteria, and the completeness of study outcome collection.

8.2 Data Storage

Data will be entered into a secure online database. All data will be maintained in the secure online database (REDCap) until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

9 Risk Assessment

9.1 Potential Risk to Participants

Anticoagulation strategy and monitoring tools vary within and across institutions. There are no randomized controlled trials evaluating safety or comparing the effect of different strategies on clinical outcomes. In this trial, two anticoagulation strategies are proposed: 1. Low intensity anticoagulation administered at doses and frequencies commonly used for DVT prophylaxis and 2. Moderate intensity anticoagulation titrated to a PTT goal of 40-60 seconds or an Anti-Xa level of 0.2-0.3 IU/mL. This first strategy of low intensity anticoagulation (a strategy congruent with usual DVT prophylaxis) is being studied in this trial with the goal of decreasing life-threatening bleeding, a common and potentially catastrophic complication during V-V ECMO. This strategy is not the standard of care. The second strategy of moderate intensity reflects usual care at our institution for patients receiving V-V ECMO at our institution; however, it has been documented that patients with a contraindication to anticoagulation (e.g. recent surgery) can be safely managed on V-V ECMO without any anticoagulation. Therefore, regardless of treatment arm, patients randomized in this study will receive an anticoagulation strategy that they may have received even if they were not included in the study and would, therefore, not experience any additional risks beyond usual care.

A potential risk to patients participating in this study involves the collection of protected health information (PHI) and the risk of loss of confidentiality. In order to limit the associated risks, the minimum amount of PHI necessary for study conduct will be collected. After collection, the data will be stored in a secure online database (REDCap) only accessible by the investigators. REDCap tools will be used to ensure that the PHI that is collected is only visible to investigators at the healthcare system where the patient as enrolled. To protect participant privacy, REDCap tools will be used to ensure that only deidentified data can be exported for use during the analyses.

9.1.1 Potential Risks of Receiving Low Intensity Anticoagulation for Patients Receiving V-V ECMO

Receiving ECMO carries risks of thromboembolism, hemolysis, consumptive coagulopathies, and circuit thrombosis. Moderate intensity anticoagulation may decrease these risks. Potential risks of receiving low intensity anticoagulation instead of moderate intensity anticoagulation include:

1) Thromboembolism – pulmonary embolism, DVT, ischemic strokes, and cardiac thrombus. The risk of thromboembolism applies to all patients receiving venovenous ECMO regardless of anticoagulation strategy but may be increased in patients who receive low intensity anticoagulation only.

2) Hemolysis – venovenous ECMO causes shear stress and mechanical trauma to red blood cells, which leads to risks of hemolysis. All patients receiving venovenous ECMO are at risk for hemolysis. If anticoagulation reduces the risk hemolysis, a less intense anticoagulation strategy may increase the risk of hemolysis.

3) Consumptive coagulopathy – the coagulation system is activated by the foreign surfaces of the ECMO circuit. This process can lead to damage and consumption of clotting factors and platelets, leading to coagulation system dysfunction. Though it has never been demonstrated, a less intense anticoagulation strategy, may exacerbate risks of consumptive coagulopathy and dysregulation of the coagulation system. Ultimately this could generate higher risks of either bleeding, clotting, or both.

2) Circuit thrombosis – fibrin and thrombus can accumulate throughout the components of the ECMO circuit (generally the oxygenator) over time due to the non-biologic surfaces of the device and turbulent areas of blood flow. The burden of thrombus may either gradually or acutely worsen requiring a controlled or emergent circuit component exchange. When a circuit component acutely fails to operate, and during any circuit component exchange, the patient may be inadequately supported by ECMO temporarily and may experience clinical compromise, including hypoxemia, acidemia, hypotension, symptomatic bradycardia, and other cardiac arrhythmias. During the majority of circuit exchanges the physiologic derangements are transient and without deleterious consequences; nevertheless, in the most severe circumstances, these may lead to cardiac arrest. All patients receiving ECMO are at risk for requiring a circuit or circuit component exchange, and circuit or circuit component exchange are frequently required for patients receiving V-V ECMO regardless of anticoagulation strategy. Compared to moderate intensity anticoagulation, a strategy of low intensity anticoagulation could increase the risk of circuit thrombosis, but based on available data, this is unknown.

9.1.2 Potential Risks of Receiving Moderate Intensity Anticoagulation for Patients Receiving V-V ECMO

One potential risk to participating in this study is receiving the moderate intensity anticoagulation strategy rather than the low intensity anticoagulation strategy. Moderate intensity could increase the risk of life-threatening bleeding relative to low intensity anticoagulation. Because moderate intensity anticoagulation is the standard strategy for patients receiving V-V ECMO at this institution, the moderate intensity anticoagulation strategy does not represent any risk beyond the risks of receiving V-V ECMO as part of usual care.

9.2 Minimization of Risk

Federal regulations at 45 CFR 46.111(a)(1) require that risks to participants are minimized by using procedures which are consistent with a sound research design. This study protocol incorporates numerous design elements to minimize risk to patients that meet this human subject protection requirement. Both low intensity and moderate intensity anticoagulation (Heparin and Bivalirudin) have been approved by the Food and Drug Administration and have been used in clinical practice during ECMO for decades with an established safety profile. Experience treating patients receiving venovenous ECMO with both low intensity and moderate intensity anticoagulation strategies has been reported in the literature. Data suggest, but do not prove, that both strategies are safe. To mitigate risk introduced by either strategy we exclude from the study patients with known allergy to heparin, patients with known or suspected active bleeding or thromboembolism and patients at higher than usual risk of bleeding or thromboembolism. Given the concerns regarding increased risk of thromboembolism among

patients with COVID-19, we also exclude patients with a positive SARS-CoV-2 test within 21 days of screening or for whom the treatment team has a high clinical suspicion for COVID-19. Furthermore, the trial specifically excludes all patients for which the treating clinicians believe a specific anticoagulation strategy is required, so all enrolled participants will be assessed safe for either treatment group by treating clinicians. Finally, at any time during the study, the treatment team may change the anticoagulation strategy if and when it is determined to be necessary for patient safety. The study protocol includes daily monitoring for protocol adherence and adverse events during the period of the study intervention.

9.3 Potential Benefit

Study participants may or may not receive any direct benefits from their participation in this study. Participants who are randomized to the moderate intensity anticoagulation group are expected to receive the anticoagulation strategy that they would receive were they to choose not to participate in the study; thus, this group is not expected to receive a direct benefit. If administration of low intensity anticoagulation improves clinical outcomes among adults receiving V-V ECMO, the participants randomized to this group may directly benefit.

9.4 Risk in Relation to Anticipated Benefit

Federal regulations at 45 CFR 46.111 (a)(2) require that “the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.” Based on the preceding assessment of risks and potential benefits, the risks to participants are reasonable in relation to anticipated benefits. Various anticoagulation strategies for patients receiving V-V ECMO have been used in clinical practice for decades. Although data do not prove safety or superiority between these strategies there are data to suggest either strategy is safe and potentially effective.

10 Human Subjects Protections

Each study participant or a LAR must sign and date an informed consent form. Approval of the Vanderbilt Institutional Review Board will be required before any participant is entered into the study.

10.1 Selection of Subjects

Federal regulations at 45 CFR 46(a)(3) require the equitable selection of participants. Every adult patient for whom V-V ECMO is initiated at Vanderbilt University Medical Center or accepted on V-V ECMO from an outside institution will be screened to determine if the patient meets inclusion and exclusion criteria. Data that have been collected as part of routine clinical care will be reviewed to determine eligibility. If any patient meets criteria for study enrollment, then the attending physician responsible for his or her care will be asked for permission to approach the patient or his or her LAR for informed consent. Study exclusion criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals for participation in the research. Hence, the recruitment of participants conforms to the principle of distributive justice.

10.2 Justification of Including Vulnerable Subjects

The present research aims to investigate the feasibility of a large multicenter trial evaluating the safety and efficacy of treating patients receiving V-V ECMO with low intensity anticoagulation. Patients receiving V-V ECMO have severe respiratory failure and are at high risk for mortality. Due to the nature of this patient population, many of these patients will have impaired decision-making capabilities. Therefore, this study would be virtually impossible to perform if only those participants with retained decision-making capacity were enrolled and would not be generalizable to the population of patients receiving venovenous ECMO. Hence, participants recruited for this trial are not being unfairly burdened with involvement in this research.

10.3 Informed Consent

Federal regulations 45 CFR 46.111(a)(5) require that informed consent will be sought from each patient or the patient's LAR. Study personnel obtaining informed consent are responsible for ensuring that the patient or LAR understands the risks and benefits of participating in the study, answering any questions the patient or LAR may have throughout the study and sharing any new information in a timely manner that may be relevant to the patient's or LAR's willingness to permit the patient's continued participation in the trial. The study personnel obtaining informed consent will make every effort to minimize coercion. Whenever possible, consent will be obtained by a study team member separate from the person who obtained consent for cannulation and initiation of ECMO. All patients or their LARs will be informed of the objectives of the study and the potential risks. The informed consent document will be used to explain the risks and benefits of study participation to the patient or LAR in simple terms and to confirm that the patient or LAR is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study before the patient is entered into the study. The investigator is responsible for ensuring that informed consent is given by each patient or LAR. This includes obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures including initiation of study intervention. If the potential participant is under the care of another physician (not the Investigator), the patient's physician will approach the patient first and obtain permission from the patient to be approached by the Investigator regarding the research opportunity.

10.4 Continuing Consent

Patients for whom consent was initially obtained from a LAR, but who subsequently regain decision-making capacity while in hospital will be approached for consent for continuing participation, including continuance of data acquisition. The consent form signed by the LAR should reflect that such consent should be obtained.

10.5 Withdrawal of Consent

Participating patients may withdraw or be withdrawn (by the LAR, treating physician, or investigator) from the trial at any time without prejudice. Data recorded up to the point of withdrawal will be included in the trial analysis, unless consent to use data has also been withdrawn. Withdrawal of consent prior to receipt of the study intervention will constitute a screen-failure and will be recorded. Withdrawal of consent after randomization and initiation of the study intervention will lead to discontinuation of study interventions, but site staff will request access to medical records for data related to the trial.

10.6 Identification of Legally Authorized Representatives

Many of the patients approached for participation in this research protocol will have impaired decision-making capacity due to critical illness and will not be able to provide informed consent. Accordingly, informed consent will be sought from the patient's LAR.

Regarding consent from the LAR, the existing federal research regulations ('the Common Rule') states at 45 CFR 46.116 that "no investigator may involve a human being as a subject in research…unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative"; and defines at 45 CFR 46 102 (c) a LAR as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the research." The Office of Human Research Protections (OHRP) defined examples of "applicable law" as being state statutes, regulations, case law, or formal opinion of a State Attorney General that addresses the issue of surrogate consent to medical procedures. Such "applicable law" could then be considered as empowering the LAR to provide consent for participant participation in the research. Interpretation of "applicable law" may be state specific and will be addressed by the IRB.

According to a previous President's Bioethics Committee (National Bioethics Advisory Committee (NBAC)), an investigator should accept a relative or friend of the potential participant who is recognized as an LAR for purposes of clinical decision making under the law of the state where the research takes place.[46] Finally, OHRP has stated in their determination letters that a surrogate could serve as a LAR for research decision making if such an individual is authorized under applicable state law to provide consent for the "procedures" involved in the research study.

10.7 Justification of Surrogate Consent

According to the Belmont Report, respect for persons incorporates at least two ethical convictions; first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. One method that serves to protect patients is restrictions on the participation of patients in research that presents greater than minimal risk.

Commentators and research ethics commissions have held the view that it is permissible to include incapable participants in greater than minimal risk research as long as there is the potential for beneficial effects and that the research presents a balance of risks and expected direct benefits similar to that available in the clinical setting. Several U.S. task forces have deemed it permissible to include incapable participants in research. For example, the American College of Physicians' document allows surrogates to consent to research involving incapable participants only "if the net additional risks of participation are not substantially greater than the risks of standard treatment". Finally, NBAC stated that an IRB may approve a protocol that presents greater than minimal risk but offers the prospect of direct medical benefits to the participant, provided that "the potential subject's LAR gives permission…".

Consistent with the above ethical sensibilities regarding the participation of decisionally incapable participants in research and the previous assessment of risks and benefits in the previous section, the present trial presents a balance of risks and potential direct benefits that is similar to that available in the clinical setting.

10.8 Confidentiality

Federal regulations at 45 CFR 46 111 (a) (7) requires that when appropriate, there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data. At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. All patients will be assigned a unique study ID number for tracking. All data collected for this study will be entered directly into a secure online database. All data will be maintained in the secure online database until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

11 Adverse Events

Assuring patient safety is an essential component of this protocol. Both anticoagulation strategies have been used for decades in critically ill patients with an established safety profile. Treatment with low intensity anticoagulation for patients receiving V-V ECMO, however, raises unique safety considerations. This protocol addresses these considerations through:

1. Exclusion of patients with active bleeding and patients assessed as at high risk of bleeding (for whom the moderate intensity anticoagulation strategy might be unsafe);
2. Exclusion of patients with active thromboembolism or patients felt to be at high risk of thromboembolism (for whom the low intensity anticoagulation strategy might be insufficient);
3. Proactive education of treating clinicians regarding signs of oxygenator inefficiency and failure and ECMO circuit component thrombosis;
4. On-study monitoring of circuit components for signs of thrombosis and oxygenator insufficiency/failure;
5. Systematic collection of safety outcomes relevant to anticoagulation strategy during V-V ECMO;
6. Structured reporting of adverse events

11.1 Adverse Event Definitions

Adverse Event: Any untoward medical occurrence associated with the use of a drug or a study procedure, whether or not considered drug related.

Serious Adverse Event: A serious adverse event is any adverse event that results in one of the outcomes listed in section 11.3 below.

Adverse Reaction: An adverse reaction means any adverse event caused by a study intervention. An adverse reaction is a subset of all suspected adverse events where there is a reason to conclude that the study intervention caused the event.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the study procedures caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the study procedures and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction.

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction that is both unexpected (not consistent with risks outlined in the study protocol or investigator brochure), serious, and meets the definition of a suspected adverse reaction.

11.2 Safety Monitoring

Assuring patient safety is an essential component of this protocol. Site investigators have primary responsibility for the safety of the individual patients enrolled at their respective institutions. Each investigator has primary responsibility for the safety of the individual participants under his or her care. The Investigators will evaluate patients for protocol adherence and adverse events daily from **enrollment through 24 hours after the end of the intervention period** (the first of diagnosis of a major bleeding event, diagnosis of a thrombotic event, placement of an arterial ECMO cannula, decannulation from ECMO, or death). If adverse events are identified, site investigators will determine if such adverse events are reportable. Thereafter, adverse events are not required to be reported unless the investigator feels the adverse event was definitely or possibly related to study intervention or procedures.
Serious adverse events that are definitely or probably related to study procedures will be considered reportable and thus collected in the adverse events case reports forms.
Investigators 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 investigator that the experience is definitely related to study procedures.
- Probably 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" 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.

Serious adverse events that are definitely or probably related to study procedures will be collected from randomization until death or discharge.

11.3 Serious Adverse Events

Serious adverse event collection begins after randomization and study procedures have been initiated. If a patient experiences a serious adverse event after consent, but prior to randomization or starting study procedures, the event will NOT be collected.

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
- Persistent or significant disability/incapacity

Reportable serious adverse events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Clinical Outcomes. 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. Death and organ dysfunction will be reported as outcomes and not as AEs unless the treating clinician or study personnel believe the event is related or potentially related to the study OR is more severe or prolonged than expected. This approach—considering death and organ dysfunction as outcomes rather than AEs and systemically collecting these 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 AE reporting to identify these important events. The following is a list of items that will be systematically collected as primary or secondary clinical outcomes. These will not be reported as AEs during this study, unless determined by treating clinicians or study personnel to be related or potentially related to the study or more severe or prolonged than expected:

1. Death (all deaths occurring prior to hospital discharge will be reported on the eCRF in the vital status at hospital discharge section)
2. Major or minor bleeding
3. Thromboembolic event
4. Cannula-associated DVT
5. Hemolysis
6. Thrombocytopenia
7. Heparin-induced thrombocytopenia
8. ECMO circuit or circuit component thrombosis
9. Renal Failure
10. Duration of ECMO support, ECMO recannulation
11. Duration of ICU admission, ICU readmission
12. Duration of hospitalization, hospital readmission

Communication and Reporting of Adverse Events. In order to ensure proper and timely reporting of reportable adverse events, there will be a clear communication plan for all study personnel to follow. Site investigators must alert the principal investigator of any **serious adverse event that is definitely or possibly related to study procedures** within 24 hours of investigator awareness of the event. Alerts issued via telephone are to be immediately followed with official notification on the adverse event case report form. The principal investigator or a delegate will report all unexpected deaths, serious adverse events that are definitely or probably related, and SUSARs to the IRB within 7 calendar days of the Investigator's knowledge of the event.

12 Statistical Considerations

12.1 General Considerations

We will present summary tabulations by treatment group. For categorical variables, the number and percentage of patients within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of patients, median and interquartile range as appropriate, will be presented.

12.2 Analysis Populations

The intent-to-treat (ITT) population will be the primary outcome analysis population. Patients who meet any exclusion criterion will not be a part of the ITT population and will be considered screening failures. Any patient who is randomized will be considered part of the ITT population.

12.3 Statistical Analysis

Descriptive statistics including mean, median, standard deviation, and interquartile range will be used to analyze continuous variables and frequency and percentage for categorical variables and binary outcomes. A pilot trial is not a hypothesis testing study and is unable to provide a preliminary test for the hypothesis.[23-25] Therefore, variables will be described and presented, and no inferential statistical tests will be performed.

12.4 Sample Size

Given their small size, pilot trials have limited ability to estimate effect sizes that will be observed in subsequent large trials trial[23,24,26]. As this is a descriptive pilot, feasibility trial, no formal sample size calculation has been undertaken. We will plan to enroll to the first of 30 total patients across all sites or up to November 12, 2023

13 Privacy and Confidentiality

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. All patients will be assigned a unique study ID number for tracking. Data collected from the medical record will be entered into the secure online database REDCap. All data will be maintained in the secure online database REDCap until the time of study publication. REDCap tools will be used to ensure that only deidentified data can be exported from the online database for analysis. At the time of publication, all links to identified data will be deleted.

14 Follow-up and Record Retention

Patients will be followed after enrollment until hospital discharge. Data collected from the medical record will be entered into the secure online database REDCap. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified version of the database will be generated and PHI will be destroyed.

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