VUMC Institutional Review Board
Informed Consent Document for Research

Study Title: Strategies For Anticoagulation During Venovenous ECMO: The SAFE-ECMO Pilot Trial
Version Date: 5/13/22
PI: Whitney Gannon, MSN, MS

Name of participant:_____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

Key Information:
The first section of this document contains some key points that the research team thought you would find important. The study is described in more detail after this section. If you do not understand something, please ask someone.

Key information about this study:
You are being asked to take part in this research study because you are receiving Extracorporeal Membrane Oxygenation (ECMO) for severe respiratory (lung) failure. The ECMO device circulates the blood outside the body through a machine, which affects the blood clotting system and creates risks of both clotting and bleeding complications. In order to reduce clotting complications, patients receiving ECMO for respiratory failure are usually given an anticoagulant (blood thinner). We do not know which dose of anticoagulant is best for balancing the risks of bleeding. Using higher doses of anticoagulation may increase the risk of life-threatening bleeding. Using lower doses may increase the risk of blood clots including strokes and potentially dangerous clots in the ECMO circuit.

While you are in this study, you will receive one of two anticoagulant strategies. One strategy involves giving a lower dose anticoagulant under the skin (lowintensity anticoagulation). The other involves giving a moderate dose anticoagulant (moderate intensity anticoagulation), which is usually administered continuously through an intravenous line. You will receive the assigned anticoagulant until you are taken off ECMO, or until you have a reason to change anticoagulant strategy (like bleeding or clotting). All other aspects of your medical care will be directed by the team taking care of you in the hospital. At any time, your team can change your anticoagulant strategy if they think a specific regimen is needed for your medical care or safety. You may withdraw from this study at any time.

Study Title: Strategies For Anticoagulation During Venovenous ECMO: The SAFE-ECMO Pilot Trial
Version Date: 5/13/22
PI: Whitney Gannon, MSN, MS

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

You are being asked to take part in this research study because...
We do not know which dose of anticoagulant is best for balancing the risks of bleeding and clotting during ECMO for respiratory failure. Currently, most patients receive moderate intensity anticoagulation through continuous administration of an intravenous anticoagulant, although some patients do receive the lower dose of anticoagulant under the skin. Using a lower dose anticoagulant under the skin may reduce the risk of life-threatening bleeding, but it could increase the risk of life-threatening blood clots in the ECMO circuit or in your body (such as a stroke or clots in the lungs). We do not know whether using a lower dose anticoagulant is overall helpful, overall harmful, or has no effect during ECMO for respiratory failure.

The purpose of this study is to collect information needed to determine if the anticoagulant strategy affects the chance of experiencing either bleeding or clotting during ECMO. We expect to ask every patient who undergoes venovenous ECMO during the 12 months of this study at Vanderbilt University Medical Center to participate.

You do not have to be in this research study. You may choose not to be in this study without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Side effects and risks that you can expect if you take part in this study:

Risks of Anticoagulation Regardless of Treatment Arm:
Both treatment arms include some form of anticoagulation and all patients in the study will be receiving ECMO. Bleeding and clotting are known risks of ECMO, and all forms of anticoagulation increase risks for bleeding and are intended to reduce risks of clotting. We do not know if the risks of bleeding and clotting are higher or lower in either treatment group. When receiving an anticoagulant, it may take you longer than usual to stop bleeding and you may bruise and/or bleed more easily when treated with anticoagulants. Bleeding can occur at virtually any site and fatal bleeding can occur. All anticoagulants have also been associated with a risk of anemia (low blood counts) and thrombocytopenia (low platelet counts).

Possible Risks of a Low Intensity Anticoagulation Strategy:
Compared to moderate intensity anticoagulation (the most commonly administered anticoagulation strategy at Vanderbilt University Medical Center outside of a clinical trial), a strategy of low intensity anticoagulation may be associated with a higher risk of clotting events, such as stroke, pulmonary embolism, myocardial infarction, arterial

Study Title: Strategies For Anticoagulation During Venovenous ECMO: The SAFE-ECMO Pilot Trial
Version Date: 5/13/22
PI: Whitney Gannon, MSN, MS

embolism leading to loss of arm or leg, clotting of the ECMO circuit that requires emergent exchange of the ECMO circuit, or a blood clot leading to death. The risk of serious and life-threatening bleeding, however, is expected to be lower with a low intensity anticoagulation strategy than with a moderate intensity anticoagulation strategy.

Low intensity anticoagulation (which unlike moderate intensity anticoagulation is administered under the skin) has an increased risk of hematoma (bruises) at the injection site (9%), bleeding at the injection site (3% to 5%), or pain at the injection site (2%).

Your treatment team will choose one of the following commonly used medication and doses to achieve low intensity anticoagulation. All of these medications are approved by the Federal Drug Administration (FDA) and commonly used at the listed doses and routes to prevent blood clots for critically ill adults.

- Heparin sodium
  - Route: subcutaneous (injection into the skin tissue)
  - Dose: 5,000 units to 7,5000 units every 8 or 12 hours
  - Medication-specific side effects:
    - Heparin-induced thrombocytopenia (HIT): there is risk of HIT which is an antibody-mediated reaction that may progress to the development of venous and arterial clots, a condition known as heparin-induced thrombocytopenia and thrombosis (HITT).
    - Hypersensitivity (allergic reactions): generalized hypersensitivity reactions have been reported with fevers, chills, and hives as the most usual manifestations; asthma, runny nose, tearing, headache, nausea, vomiting, and life-threatening allergic reactions occur rarely
- Enoxaparin
  - Route: subcutaneous (injection into the skin tissue)
  - Dose: 30mg to 40mg every 12 or 24 hours
  - Medication-specific side effects:
    - Heparin-induced thrombocytopenia (HIT): there is risk of HIT which is an antibody-mediated reaction that may progress to the development of venous and arterial clots, a condition known as heparin-induced thrombocytopenia and thrombosis (HITT)
    - Hypersensitivity (allergic reactions): generalized hypersensitivity reactions have been reported with fevers, chills, and hives as the most usual manifestations; asthma, runny nose, tearing, headache, nausea, vomiting, and life-threatening allergic reactions occur rarely
- Fondaparinux
  - Route: subcutaneous (injection into the skin tissue)
  - Dose: 2.5mg to 10mg daily every 24 hours
  - Medication-specific side effects:
    - Hypersensitivity (allergic reactions): generalized hypersensitivity reactions have been reported such as fever, nausea, constipation, rash, vomiting, insomnia, low potassium, urinary tract infection, dizziness, purpura, hypotension, confusion, urinary retention, headache, pain

Study Title: Strategies For Anticoagulation During Venovenous ECMO: The SAFE-ECMO Pilot Trial
Version Date: 5/13/22
PI: Whitney Gannon, MSN, MS

Possible Risks of a Moderate Intensity Anticoagulation Strategy:
Compared to low intensity anticoagulation, moderate intensity anticoagulation (the most commonly administered anticoagulation strategy at Vanderbilt University Medical Center outside of a clinical trial) may have higher risk of bleeding events, including life-threatening bleeding or bleeding in sensitive areas like into the brain (hemorrhagic strokes). Moderate intensity anticoagulation is the usual anticoagulation strategy for patients who receive ECMO at Vanderbilt University Medical Center. If you are assigned to this group, the potential risks are the same risks you would expect to experience if you choose not to be in this study.

Your treatment team will choose one of the following commonly used medication and doses to achieve moderate intensity anticoagulation. All of these medications are approved by the Federal Drug Administration (FDA) and commonly used at the listed doses and routes to prevent blood clots for critically ill adults receiving ECMO.

- Heparin sodium
  - Route: continuously infusion through a catheter in your vein (IV catheter)
  - Dose: 100units/hr to 2,000units/hr titrated to target a PTT of 40-60 seconds or anti-xa level of 0.2 to 0.3 IU/mL
  - Medication-specific side effects:
    - Heparin-induced thrombocytopenia (HIT): there is risk of HIT which is an antibody-mediated reaction that may progress to the development of venous and arterial clots, a condition known as heparin-induced thrombocytopenia and thrombosis (HITT)
    - Hypersensitivity (allergic reactions): generalized hypersensitivity reactions have been reported with fevers, chills, and hives as the most usual manifestations; asthma, runny nose, tearing, headache, nausea, vomiting, and life-threatening allergic reactions occur rarely
- Enoxaparin
  - Route: subcutaneous (injection into the skin tissue)
  - Dose: 50 mg to 180 mg titrated to target an anti-xa level of 0.2 to 0.3 IU/mL daily every 12 or 24 hours
  - Medication-specific side effects :
    - Heparin-induced thrombocytopenia (HIT): there is risk of HIT which is an antibody-mediated reaction that may progress to the development of venous and arterial clots, a condition known as heparin-induced thrombocytopenia and thrombosis (HITT)
    - Hypersensitivity (allergic reactions): generalized hypersensitivity reactions have been reported with fevers, chills, and hives as the most usual manifestations; asthma, runny nose, tearing, headache, nausea, vomiting, and life-threatening allergic reactions occur rarely
- Bivalirudin
  - Route: continuously infusion through a catheter in your vein (IV catheter)
  - Dose: 0.1mg/kg/hr to 2 mg/kg/hr titrated to target a PTT of 40 to 60 seconds
  - Medication-specific side effects:
    - Hypersensitivity (allergic reactions): generalized hypersensitivity reactions have been reported such as fever, nausea, vomiting, urinary retention, back pain, insomnia, anxiety, nervousness, low blood pressure, and headache

Study Title: Strategies For Anticoagulation During Venovenous ECMO: The SAFE-ECMO Pilot Trial
Version Date: 5/13/22
PI: Whitney Gannon, MSN, MS

Risks that are not known:
There may be risks associated with either a low intensity anticoagulation strategy or a moderate intensity anticoagulation strategy that we do not know about at this time.

Good effects that might result from this study:
Although we do not know if either group is overall helpful, overall harmful, or if the groups are equivalent, it is possible that you might benefit from the study by being assigned to a group that is ultimately found to provide a benefit (for example by reducing the risk of life-threatening bleeding). In addition, the study mightprovide benefits to science and humankind as the results gained from you being in this study may help others in the future who receive ECMO for respiratory failure.

Study Title: Strategies For Anticoagulation During Venovenous ECMO: The SAFE-ECMO Pilot Trial
Version Date: 5/13/22
PI: Whitney Gannon, MSN, MS

Procedures to be followed:
You will be asked to follow the instructions from the study doctor and study staff.

Study Procedure 1: Consent for Study Participation	
Timing	Today
Explanation	Consent includes reading through this form, asking questions, and receiving answers.
Risks or Discomforts	You may not understand all the information in this form. Please be sure to ask questions so you understand.
What you will do	After reading this form and asking questions, if you agree to be in this research study, you will sign this form.
What we will do	We will go through this form with you, answer any questions you have, and give you a copy of the consent form.

Study Procedure 2: Randomization	
Timing	Today (following signing of consent)
Explanation	If you agree to be in this study, you would be assigned to one of two groups: The **Low Intensity Anticoagulation Group** or the **Moderate Intensity Anticoagulation Group**. You would be assigned randomly, like the flip of the coin. This is called randomization and is done by a computer program.
Risks or Discomforts	You will receive low intensity anticoagulation or the moderate intensity anticoagulation. Both are explained below
What you will do	Agreeing to be in this study includes knowing that you will be assigned to one group or the other. You will not be able to pick which group you are in. You will not be able to change groups unless your medical team thinks you need to change groups for your medical care or safety.
What we will do	We will communicate with your doctors and nurses regarding which anticoagulation strategy you will receive. Your doctors and nurses will know which strategy you are receiving and will be able to change it at any time if needed for your medical care or safety.

Study Title: Strategies For Anticoagulation During Venovenous ECMO: The SAFE-ECMO Pilot Trial
Version Date: 5/13/22
PI: Whitney Gannon, MSN, MS

Study Procedure 3: Anticoagulation strategy	
Timing	Every day from today until you are removed from ECMO or experience a clot or significant bleeding
Explanation	All patients on ECMO receive an anticoagulant every day they are on ECMO, unless they have a reason that they cannot receive an anticoagulant (bleeding). The dose of anticoagulant you receive will be determined by the study and will be given according to hospital protocols and monitored by your doctors and nurses. You will receive the anticoagulant, using the strategy determined by the study, every day until you come off ECMO, or an event occurs that leads your doctors to change your anticoagulant strategy, like bleeding, clotting, or some other event that changes the risk of anticoagulation. At any time in the study, your doctors can change the anticoagulation if needed for your medical care or safety.
Risks or Discomforts	**Low Intensity Anticoagulation Group**: See "Possible Risks" section above. In this group patients receive a lower dose of anticoagulant under their skin between one and three times daily. This anticoagulation treatment is expected to provide less blood thinning effect than the moderate intensity anticoagulation strategy, which could increase the risk for clotting during ECMO. **Moderate Intensity Anticoagulation Group:** See "Possible Risks" section above. In this group patients receive a continuous infusion of an anticoagulant, and the dose is adjusted based on blood tests. This is the usual anticoagulation strategy for most patients who receive ECMO at Vanderbilt University Medical Center. If you are assigned to this group, the potential risks are the same risks you would expect to experience if you choose not to be in this study. **Regardless of whether you participate in this study, your doctors will give you an anticoagulant while you are on ECMO, unless you develop a reason it cannot be given (like bleeding). Bleeding and clotting sometimes happen to patients on ECMO and may happen no matter what anticoagulation strategy is used. We do not know whether the risks of bleeding or clotting are different between these two groups.
What you will do	Nothing for you to do. The medications will be administered by your nurse.
What we will do	While you are receiving the assigned anticoagulant strategy, we will check on you daily to see how you are doing, help make sure you are getting the assigned anticoagulant strategy, and look for any new conditions that might lead your doctors to change the anticoagulant strategy (bleeding or clotting).

Study Title: Strategies For Anticoagulation During Venovenous ECMO: The SAFE-ECMO Pilot Trial
Version Date: 5/13/22
PI: Whitney Gannon, MSN, MS

Study Procedure 4: Medical Record Review	
Timing	Today, and until the end of your hospital admission.
Explanation	Data will be collected from your medical record. These data will include: demographics like age, race, and sex; your health history, information from this hospital stay like diagnosis, treatments, laboratory test results, medications, how long you are on ECMO and in the hospital, and how well you respond to treatment.
Risks or Discomforts	There is a small risk that some of your personal health information will be exposed.
What you will do	Nothing for you to do.
What we will do	We will take information from your medical record and enter it into a secure study database. We will take steps to prevent your data from being improperly exposed. These steps include: all data will be coded in the final data base so information will not directly identify you; only researchers involved with this study will have access to the secure database with your personal information.

Payments for your time spent taking part in this study or expenses:
You will not receive payment for your participation in this study.

Costs to you if you take part in this study:
If you agree to take part in this research study, you and/or your insurance will not have to pay for the tests and treatments that are being done only for research. However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

You have the right to ask what it may cost you to take part in this study. If you would like assistance, financial counseling is available through the Vanderbilt Financial Assistance Program. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs and your doctor will discuss other treatment plans with you.

Study Title: Strategies For Anticoagulation During Venovenous ECMO: The SAFE-ECMO Pilot Trial
Version Date: 5/13/22
PI: Whitney Gannon, MSN, MS

Payment in case you are injured because of this research study:
If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate **medical** care provided **at Vanderbilt** to treat the injury.

There are no plans for Vanderbilt 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 Vanderbilt to give you money for the injury.

Who to call for any questions or in case you are injured:
If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact:

Whitney Gannon at 610-909-5789

If you cannot reach the study doctor at this number, please page the study doctor at **615-835-8431.**

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the VUMC Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

Reasons why the study doctor may take you out of this study:
The study doctor may take you out of the study if he or she thinks it is not in your best interest.

What will happen if you decide to stop being in this study?
If you decide to stop being part of the study, you should tell your study doctor or study staff. These people will talk to you about the study and will remove you from the study if you would like to be removed. Deciding to not be part of the study will not change your regular medical care in any way.

Clinical Trials Registry:
A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. The website will include a summary of the results within one year of completing the study. You can search this Web site at any time.

Confidentiality:
Vanderbilt University Medical Center may share your information without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt University Medical Center, Dr. Casey, and his staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

Study Title: Strategies For Anticoagulation During Venovenous ECMO: The SAFE-ECMO Pilot Trial
Version Date: 5/13/22
PI: Whitney Gannon, MSN, MS

It is the intent of the study doctor, study staff, and Vanderbilt that the health data that is sent for use in other research studies will not identify you.

You will not be identified by name in any published reports about this study or in any other scientific publication or presentation. If you think that you were harmed from being in the study, the study team may also share health data about you with the Vanderbilt's insurer to resolve your claim.

Vanderbilt may use the health data obtained during the study:

- To develop new tests
- For other activities (such as development and regulatory)
- As part of research activities related to the study of diseases and the development of drugs and tests used to treat diseases.
- To allow outside researchers to use clinical data that does not identify you.

For these uses, Vanderbilt may share this health data with others involved in these activities, as long as they agree to only use the health data as described here. Vanderbilt may transfer health data about you from your country to other countries where the privacy laws may not be as strict. Once the research team shares health data about you with others, it may no longer be protected by privacy laws.

There is a risk that if people outside the study get your health data they could misuse it for purposes other than those outlined in this consent. The study team has strict privacy and confidentiality protection procedures in place to prevent this from occurring so the chance of this happening to you is extremelysmall.

This study may have some support from the National Institutes of Health (NIH). If so, your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to reportby law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

Privacy:
Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefitas a result of the tests done on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Study Title: Strategies For Anticoagulation During Venovenous ECMO: The SAFE-ECMO Pilot Trial
Version Date: 5/13/22
PI: Whitney Gannon, MSN, MS

Study Results:
The results of this study will be presented publicly and published. You will not be identified. Study results will not be shared directly with participants but will be available through www.clinicaltrials.gov.

Authorization to Use/Disclose Protected Health Information

What information is being collected, used, or shared?
To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Vanderbilt University Medical Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use or share the information?
The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical Center. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this Authorization?
You do not have to sign this Authorization, but if you do not, you may not join the study.

How long will your information be used or shared?
Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?
You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

Study Title: Strategies For Anticoagulation During Venovenous ECMO: The SAFE-ECMO Pilot Trial
Version Date: 5/13/22
PI: Whitney Gannon, MSN, MS

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____ _____
Date Signature of patient/volunteer

Consent obtained by:

_____ _____
Date Signature

_____
Printed Name and Title

Time: _____

Institutional Review Board Informed Consent Document for Research

Principal Investigator: Jonathan Casey, MD, MSCI **Version Date:** 3/9/2021
Study Title: Strategies For Anticoagulation During Venovenous ECMO: The SAFE-ECMO Pilot Trial
Institution/Hospital: Vanderbilt University Medical Center

I,_____ [name of decision-maker/surrogate],
am the _____ [state relationship to participant]
of _____ [state participant's name]. I have read the

informed consent document or it has been explained to me. I have had the opportunity to ask any questions and all of my questions have been answered. I have been informed that an investigational treatment may be administered to_____[participant's name]. I believe receiving such treatment would be in the interests of _____ [participant's name] and is consistent with what he/she would have decided had he/she been able to do so.

Your decision to allow your family member/friend to participate in this research study is voluntary. You may choose not to allow his/her participation and he/she will receive alternative treatments without affecting his/her healthcare/services or other rights. You are also free to withdraw him/her from this study at any time. In the event new information becomes available that may affect the risks or benefits associated with this research study or your willingness to allow continued participation in this research study, you will be notified so that you can make an informed decision whether or not to continue your family member/friend's participation in this study.

Your family member/friend will periodically be re-evaluated for the capacity to give consent. If he/she is found to be capable, continued participation in this study would only occur with his/her consent.

_____ ___/___/___
Signature of Health Care Decision-Maker/Surrogate Date

_____ ___/___/___
Signature of Witness Date

_____ ___/___/___
Name and Signature of person obtaining consent Date

Date of IRB Approval: 03/28/2023
Date of Expiration: 03/27/2024

Institutional Review Board
VANDERBILT