Study Title: A Pilot Study in Feasibility and Safety: Point of Care testing with thromboelastography (TEG) for blood product transfusion and coagulation in patient's requiring extracorporeal membrane oxygenation (ECMO)

Principal Investigator: Stephen Esper, MD, MBA

Document: Study Protocol
Document Date: 29 AUG 2019

NCT #: NCT02887820
STUDY #: STUDY19070239

Basic Study Information

1. * **Title of study:**
A Pilot Study in Feasibility and Safety of Point of care testing with thromboelastography (TEG) for blood product transfusion and anticoagulation in patients requiring Extracorporeal Membrane Oxygenation (ECMO)

2. * **Short title:**
Evaluate the feasibility of following TEG algorithm in patients requiring ECMO

3. * **Brief description:**
This is a pilot study that seeks to evaluate the feasibility and safety of using a TEG algorithm in addition to traditional laboratory tests to guide transfusion and anticoagulation management of ECMO patients. Patients requiring ECMO exhibit a high risk of mortality due to bleeding and thrombosis, as the non-biological surface of the extracorporeal surface activates both procoagulant and anticoagulant mechanisms (1). Using TEG as a point-of-care device to provide individualized, goal-directed therapy in this population may help decrease blood product transfusion and lead to improved blood management overall.
All adult patients requiring ECMO will be considered for the trial, with a target enrollment of 50 participants over a two-year period. For each enrolled participant, a TEG transfusion algorithm will be followed for patients exhibiting inadequate hemostasis in the operating room (Flowchart 1), and then a second TEG algorithm will be followed in the ICU when hemostasis is normal and heparin is introduced (Flowchart 2). Statistical analysis of the feasibility and compliance of using a TEG algorithm will determine the likelihood of exploring future clinical trials involving TEG-driven coagulation and transfusion management of the ECMO population.

4. * **What kind of study is this?**
Single-site study

5. * **Will an external IRB act as the IRB of record for this study?**
○ Yes ● **No**

6. * **Local principal investigator:**
Stephen Esper

* **Is this your first submission, as PI, to the Pitt IRB?**
○ Yes ○ No

7. * **Does the local principal investigator have a financial interest related to this research?**

○ Yes ● **No**

8. **Attach the protocol:**

- Sponsor/Multicenter/Investigator-initiated protocol
- Coordinating Center supplement
- Emergency Use Consent/ Protocol/ FDA Form 3926
- Exempt Application form

Document	Category	Date Modified	Document History

There are no items to display

View: Pitt SF: Funding Sources (not integrated with Grants)

Funding Sources

1. * **Indicate all sources of support:**
   External funding

2. * **Identify each organization supplying funding for the study:**

Funding Source	Sponsor's Funding ID	Grants Office ID	Attachments	Pitt Awardee	Grant Recipient
American Heart Association			AHA Plan		

Study Team Members

1. * **Identify each person involved in the design, conduct, or reporting of the research:**

Name	Roles	Department/School	Affiliation	Involved in Consent	Qualifications	Financial Interest
Michael Boisen	Co-investigator	U of Pgh | School of Medicine | Anesthesiology	Pitt faculty	yes	Michael Boisen, MD, Assistant Professor of Anesthesiology-Co-investigator, The effect of Antithrombin III on morbidity and mortality in patients und... view all	no
Jonathan D'Cunha	Co-investigator	U of Pgh | School of Medicine | Cardiothoracic Surgery	Pitt faculty	yes	Jonathan D'Cunha, MD, Visiting Associate Professor of Surgery; Surgical Director of Lung Transplantation; Vice Chairman Academic Affairs and Educatio... view all	no
Melanie Driscoll	Secondary Study Coordinator	U of Pgh | School of Medicine | Medicine	Pitt staff	yes	Melanie Driscoll is a research coordinator with the Department of Anesthesiology	no
Stephen Esper	Principal Investigator	U of Pgh | School of Medicine | Anesthesiology	Pitt faculty	yes	Stephen A. Esper, MD, MBA Assistant Professor of Anesthesiology-Co-Investigator, Remifentanil to control hyperglycemia in cardiac surgery	no
Arman Kilic	Co-investigator	Physician Services Division (UPP and CMI) | UPP | Cardiovascular Institute	Pitt faculty	yes	Arman Kilic, MD, Assistant professor of cardiothoracic surgery at the University of Pittsburgh School of	no

Name	Roles	Department/School	Affiliation	Involved in Consent	Qualifications	Financial Interest
					Medicine and director of surgical quality an... view all	
Robert Kormos	Co-investigator	U of Pgh | School of Medicine | Cardiothoracic Surgery	Pitt faculty	yes	Robert L. Kormos, MD, Professor of Surgery. Principal Investigator, Long-term animal survival with an implantable axial flow pump as a left ventricul... view all	no
Caroline Kostishack	Secondary Study Coordinator	Physician Services Division (UPP and CMI) | UPP | Anesthesiology and Pain Medicine	Pitt staff	yes	Caroline Stehle (nee Kostishack) is a clinical research coordinator in the Clinical Trials Program. Caroline Stehle (nee Kostishack) is qualified to ... view all	no
Amy Monroe	Primary Study Coordinator	U of Pgh | School of Medicine | Anesthesiology	Pitt staff	yes	Amy Monroe is the clinical trials program manager. Amy Monroe is qualified to assist with the informed consent process because she has completed the... view all	no
Penny Sappington	Co-investigator	U of Pgh | School of Medicine | Critical Care Medicine	Pitt faculty	yes	Penny L. Sappington, MD, Assistant Professor, Critical Care Medicine. Co-I, Ethyl Pyruvate: A Novel Treatment for Sepsis"; Co-I, HMGB1 Alteration Tig... view all	no

Name	Roles	Department/School	Affiliation	Involved in Consent	Qualifications	Financial Interest
Christopher Sciortino	Co-investigator	U of Pgh | School of Medicine | Cardiothoracic Surgery | Cardiac Surgery	Pitt faculty	yes	Christopher Sciortino, MD, PhD, FACS, Assistant Professor of Cardiothoracic Surgery at the University of Pittsburgh School of Medicine and Surgical D... view all	no
Kathirvel Subramaniam	Co-investigator	U of Pgh | School of Medicine | Anesthesiology	Pitt faculty	yes	Kathirvel Subramaniam, MD, MPH, Associate Professor of Anesthesiology- Principal Investigator, Remifentanil to control hyperglycemia in cardiac surge... view all	no
Darrell Triulzi	Co-investigator	U of Pgh | School of Medicine | Pathology	Pitt faculty	yes	Darrell J. Triulzi, MD, Professor of Pathology, Recipient epidemiology and donor study (REDSIII). This network will develop populations based outcome... view all	no

2. External team member information: (Address all study team members in item 1. above and leave this section blank)

Name	Description
There are no items to display	

3. Have you, Stephen Esper**, verified that all members of the research team have the appropriate expertise, credentials, training, and if applicable, child clearances and/or hospital privileges to perform those research procedures that are their responsibility as outlined in the IRB application?**

* ● **Yes** ○ No

Study Scope

Check all that apply

1. * Will this study actively recruit any of the following populations?

- [x] Adults with impaired decision-making capacity
- [ ] Children (under the applicable law of the jurisdiction in which the research will be conducted (<18 years for PA))
- [ ] Children who are Wards of the State
- [ ] Employees of the University of Pittsburgh/UPMC
- [ ] Medical Students of University of Pittsburgh as primary research group
- [ ] Students of the University of Pittsburgh
- [ ] Neonates of uncertain viability
- [ ] Non-viable neonates
- [ ] Non-English speakers
- [ ] Nursing home patients in the state of Pennsylvania
- [ ] Pregnant women
- [ ] Prisoners
- [ ] N/A

2. * Will any Waivers be requested?

- [x] Waiver/Alteration of Consent
- [ ] Waiver to Document Consent
- [ ] Waiver/Alteration of HIPAA
- [ ] Exception from consent for emergency research
- [ ] N/A

3. * Will this study involve any of the following?

- [ ] Specimens
- [ ] Honest Broker to provide data/specimens
- [ ] Return of Results to Subjects or Others
- [ ] Fetal tissue
- [x] N/A

4. * Will Protected Health Information be collected?

- [ ] Pitt medical records
- [x] UPMC medical records
- [ ] Other Institutions' medical records
- [ ] N/A

5. * Other Requests?

- [ ] Deception (if not Exempt, also requires Waiver/Alteration of Consent)
- [ ] Emergency Use / Single Patient Expanded Access (using FDA Form 3926)

- [ ] Placebo Arm
- [ ] Withdraw from usual care
- [x] N/A

6. * **Determining Scientific Review:**
Department Scientific Review (this option MUST be picked if there is DoD funding)

   * **Choose the appropriate organization to conduct the scientific review:**
U of Pgh | School of Medicine | Anesthesiology

7. * **Has this study (or substantially similar study) been previously disapproved by the Pitt IRB or, to your knowledge, by any other IRB?**
○ Yes ● **No**

> *Review the HRPO policy, if participating in research at the VA Pittsburgh Healthcare System or using funding from the VA*

8. * **Does the study use an approved drug or biologic, use an unapproved drug or biologic, or use a food or dietary supplement to prevent, diagnose, cure, treat, or mitigate a disease or condition?**
○ Yes ● **No**

9. * **Does the study evaluate the safety or effectiveness of a device (includes in-vitro laboratory assays)?**
○ Yes ● **No**

10. * **Is this application being submitted to convert an approved study from OSIRIS to PittPRO?** (Tip Sheet)

● **Yes** ○ No

> *Download the OSIRIS Transition Continuing Review form, complete and upload below. If you need to attach any additional documents (e.g., data and safety monitoring reports), upload in the Local Supporting Documents page and note the Renewal on the form.* ***Exempt*** *submissions in OSIRIS also need to move into PittPRO if they remain ongoing. These will not be considered transitions but new studies. Therefore, Study Scope #10 will be answered as "No." Once the new exempt determination has been issued, the OSIRIS application can be closed. Any exempt submission remaining in OSIRIS by the end of August 2020 will be closed by our office. Please use the "Add Comment" to provide the OSIRIS study number.*

OSIRIS Transition Continuing Review form:
Continuing Review Form 2019(0.03)

* **OSIRIS ID**
PRO16060542

11. * **Does your research protocol involve the evaluation or use of procedures that emit ionizing radiation and, after reviewing this HUSC guidance, does your research protocol require HUSC review? (If yes, upload the HUSC form in the Local Supporting Documents section). If you are unsure of review**

requirement, select yes.

○ Yes ● **No**

Research Sites

1. **Choose all sites that apply:**
   UPMC

   * **Select the UPMC sites where research will be conducted:**
   Presbyterian

2. **Describe the availability of resources and the adequacy of the facilities to conduct this study:**
   UPMC Presbyterian is a hospital with an Acute Interventional Perioperative Pain Service (AIPPS). The anesthesiologists here routinely participate in clinical trials and various other types of clinical research, are well acclimated to conducting clinical research with respect to good clinical practice. There are sufficient resources of manpower and supplies to conduct the study

Click **Continue** as this page was intentionally left blank.

Recruitment Methods

* **Will you be recruiting individuals for participation in this study?**
● **Yes** ○ No

1. * **Describe who will be recruiting individuals for participation for this study:**
The principal investigator or co-investigator will approach patient with the assistance of research associates or coordinators if they are conscious and obtain consent.

2. * **Select all methods to be used for recruitment:**
Directly approaching potential subjects (in-person)

3. * **Provide details on your recruitment methods:**
Patient will be identified through medical records and operative schedules to determine study eligibility. The principal investigator or co-investigator will approach patient with the assistance of research associates or coordinators if they are conscious and obtain consent. A proxy consent will be obtained in patients who are unable to provide consent.

4. * **Describe all compensation/incentives offered to participants and timing of these offers:**
Patients are not compensated for this study.

5. **Recruitment materials:** (attach all material to be seen or heard by subjects, including advertisements and scripts)

Document	Category	Date Modified	Document History
There are no items to display			

Study Aims

1. * **Describe the purpose, specific aims, or objectives and state the hypotheses to be tested:**
Specific Aim: A pilot study to evaluate the feasibility and safety of a research protocol, to evaluate the use of thromboelastography (TEG) in post cardiotomy, thoraco-abdominal, and trauma surgical patients requiring extracorporeal membrane oxygenation (ECMO). It is expected that these data will inform a large-scale clinical trial design. The safety of the TEG protocol will be based upon the amount of bleeding and thrombotic events.

   a. To determine the feasibility and adherence rates of following the protocol for this trial of TEG for ECMO, and identify potential interventions to improve adherence. This does not mean that the clinicians are subjects, as the clinicians are already well-practiced in interpreting TEG as a measure of coagulation and will be using TEG as a supplement to conventional testing as per study protocol. Further, all clinicians will follow the same TEG protocol for every patient enrolled in the trial.

   The feasibility and safety will be assessed by the number of transfusions that follow the TEG algorithm, how many patients complete the study, number of TEGs done, missing or extra TEGs, and number of re-operative events

2. * **Describe the relevant prior experience and gaps in current knowledge including preliminary data. Provide for the scientific or scholarly background for, rationale for, and significance of the research based on existing literature and how it will add to existing knowledge:**
A study by Shore-Lesserson, et al in 1999 demonstrated that in patients undergoing cardiac surgery, use of a TEG based transfusion algorithm resulted in less transfusions than a more traditional algorithm based on ACT, platelet count, prothrombin time (PT), and PTT. This result was hypothesized to be due to TEG's ability to provide qualitative assessment of factor and platelet function, rather than solely quantitative results (Shore et al). Another recent study by Weber, et al. demonstrated that the use of rotational thromboelastometry (ROTEM) to guide hemostatic component therapies was superior to laboratory coagulation testing in terms of efficacy and cost (Weber et al). It has been shown that use of ROTEM and TEG is associated with less perioperative blood loss without increases in transfusions or mortality (Tanaka et al).
   A retrospective analysis of 578 patients requiring veno-venous (VV) or VA-ECMO over the past nine year period at the University of Pittsburgh Medical Center was accomplished. Data included duration of ECMO, blood products transfused, and complications from ECMO. The data collected also detailed the transfusion of total blood products and packed red blood cells for patients on VV and VA ECMO. VA ECMO appears to be associated with the greatest amount of transfusion, especially on the day of initiation. Furthermore, in reviewing the data, it appears that the patients who required VA ECMO had a surgery, generally cardiotomy, prior to institution of VA ECMO. Resultantly, in many cases, the transfusion of blood products is generally associated with the day of the primary surgery. This preliminary

data is very important in that it is a guide for the investigators in the determination of where the greatest impact can be made in terms of reducing blood transfusion in the operative setting. Because of this data, patients s/p surgery (usually cardiotomy) appear to have higher incidence of transfusion and as a result, a protocolized and algorithmic focus is expected to yield a reduction of blood products in this patient population.

While the use of protocol driven use of TEG in CPB has been described, few studies have investigated the utility of TEG on the direction of patient care during ECMO for adult patients. We know that Point-of-care coagulation testing allows for rapid assessment and goal directed therapy. ROTEM and TEG allow for particularly rapid results by providing a picture of global coagulation status in around 20 minutes. This allows for more appropriate and timely transfusion of various blood products, including red blood cells, platelets, plasma, cryoprecipitate, and clotting factors (Tanaka et al). We believe the application of algorithmic use of TEG to management of hemostasis and anticoagulation for patients on ECMO is novel and has the potential to have a major impact on patient care.

Shore-Lesserson L, Manspeizer H, DePerio M, et al (1999) Thromboelastography-Guided Transfusion Algorithm Reduces Transfusions in Complex Cardiac Surgery. Anesth Analg 88, 312-19

Tanaka K, Bolliger D, Vadlamudi R, et al (2012) Rotational Thromboelastometry (ROTEM)- Based Coagulation Management in Cardiac Surgery and Major Trauma. J of Cardiothoracic and Vascular Anesthesia 26, 1083-93

Weber C, Gorlinger K, Meininger D, et al (2012) Point-of-Care Testing: A Prospective, Randomized Clinical Trial of Efficacy in Coagulopathic Cardiac Surgery Patients. Anesthesiology 117(3), 531-47

Study Design

1. **Total number of subjects to be enrolled at this site (enter -1 for chart reviews, banking, registries):**
   100

2. **Describe and explain the study design:**
   The proposed study design is single center, prospective, pilot clinical trial

3. **Describe the primary and secondary study endpoints:**
   Primary outcome variable- Determine the feasibility of following the protocol for this trial of TEG for ECMO.

   Secondary outcome variable- Assess clinical outcomes including the rates of transfusion, major bleeding, and major complications in patients on ECMO managed with TEG in addition to traditional laboratory measures of coagulation.

4. **Provide a description of the following study timelines:**

   Duration of an individual subject's active participation:
   30 days
   Duration anticipated to enroll all subjects:
   1 year
   Estimated date for the investigator to complete this study (complete primary analyses):
   12/1/2020

5. **List the inclusion criteria:**
   Adult patient requiring ECMO

6. **List the exclusion criteria:**
   Children less than 18 years of age

7. **Will children or any gender, racial or ethnic subgroups be explicitly excluded from participation?**
   ● **Yes** ○ No

   * **Identify the subgroups and provide a justification:**
   Children less than 18 years of age as only adults are seen at this institution

8. **Describe the power analysis used and cite your method of statistical analysis. If a power analysis is not possible, thoroughly justify the sample size required for the study, including appropriate literature citation (alternatively provide page reference in attached protocol):**
   Approximately 100 ECMO cases are seen per year in the UPMC Presbyterian

Hospital, of which, approximately 50% require VA-ECMO. We expect to enroll 50-60% of those patients per year. Regarding Specific Aim 1: Feasibility will be defined by a minimum of 80% of patients who will have followed the algorithm on greater than or equal to 90% of the days on ECMO.The data obtained from this pilot and feasibility study will help to establish event rates, transfusion rates and volumes, to inform subsequent larger clinical trialsIncidence of protocol compliance will be analyzed by Chi Square test or Fisher exact test. P value less than 0.05 will be considered significant. Transfusion rates and volumes as well as clinical outcome rates will be analyzed by independent-sample t test or Mann Whitney U test wherever appropriate.

Cognitively Impaired Adults

1. * **Provide a justification for the inclusion of adult subjects who are unable to provide direct consent for study participation:**
   A large proportion of patients will undergo ECMO in an emergent setting, in which they themselves are unable to provide consent due to their clinical status. Once it is determined by an investigator that the patient is unable to provide consent, consent will be obtained from the patient's proxy.

2. * **Specify the criteria used to determine that a given potential adult subject is not able to provide direct consent for participation and identify who will responsible for that determination:**
   If a patient is heavily sedated, unconscious or intubated they will not be able to provide consent and a investigator will make the determination to approach the Proxy for consent.

Research Activities

1. * **Provide a detailed description of all research activities (including screening and follow-up procedures) that will be performed for the purpose of this research study. This description of activities should be complete and of sufficient detail to permit an assessment of associated risks.**
Once the patient is placed on ECMO, baseline arterial blood gas (ABG), complete blood count (CBC), fibrinogen, platelet count, aPTT, PT and TEG will be performed. Simultaneous heparinase and kaolin TEG must be performed any time a TEG is performed. Pertinent TEG results will include: heparinase-kaolin TEG maximum amplitude (MA) in millimeters (mm), heparinase-kaolin TEG r-time in seconds, heparinase-kaolin TEG alpha angle in degrees, and TEG functional fibrinogen (FLEV) MA in mm. These tests will be performed by a perfusionist in the operating room under the oversight of a co-investigator or principal investigator.

   For all patients, the above tests will be performed per the algorithm described in Flowcharts 1 and 2 (attached). Flowchart 1 describes transfusion algorithm for patients in the operating room with inadequate hemostasis, >4 cc/kg/hour. Flowchart 2 describes transfusion management in the ICU when bleeding is less than <4 cc/kg/hour.

   Once patient has a normal TEG result with adequate hemostasis, either heparin or bivalirudin will be used as the anticoagulant. Transfusion parameters as described above will only be used on patients who are received no anticoagulation or heparin anticoagulation. If patients are receiving bivalirudin as their anticoagulation strategy, the transfusion parameters with TEG application will not apply.

   Heparin titration will be based on kaolin TEG r-time, MA, alpha angle and anti-xa. Transfusion parameters will be based on heparinase TEG results, INR, platelet count, fibrinogen, and CBC per study protocol.

   CTICU heparin titration nomogram:

   antiXa/TEG/ACT Action

   ≤0.20 units/ml and r-time < 10 minutes
   -Increase infusion rate by 2 units/kg/hour
   -Repeat STAT anti-Xa/TEG 6 hours after rate change
   **If the anti-Xa AND TEG do not agree, contact investigator and defer to anti-Xa nomogram for treatment

   0.21-0.24 units/ml and
   r-time >10 minutes but ≤15 minutes -Increase infusion rate by 1 units/kg/hour
   -Repeat STAT anti-Xa/TEG 6 hours after rate change
   **If the anti-Xa AND TEG do not agree, contact investigator and defer to anti-Xa nomogram for treatment

0.25-0.35 units/ml and r-time >15 but less than 25 minutes and angle between 20 and 50
(therapeutic range) -No changes in infusion rate
-Repeat STAT anti-Xa/TEG every 6 hours for two consecutive results
If therapeutic, order STAT anti-Xa/TEG daily
**If the anti-Xa AND TEG do not agree, contact investigator and defer to anti-Xa nomogram for treatment

0.36-0.45 units/ml and r-time >25 minutes and angle <30 -Decrease infusion rate by 1 unit/kg/hour after this hour
-Repeat STAT anti-XaTEG 2 hours after rate change
**If the anti-Xa AND TEG do not agree, contact investigator and defer to anti-Xa nomogram for treatment

0.46-0.069 units/ml and r-time >30 minutes and angle < 25 -Hold heparin infusion for 1 hour
-Decrease Infusion rate by 2 units/kg/hour after this hour
-Repeat STAT anti-Xa/TEG 2 hours after rate change
**If the anti-Xa AND TEG do not agree, contact investigator and defer to anti-Xa nomogram for treatment

≥ 0.70 units/ml and no sign of TEG clotting -Hold heparin infusion for 2 hours
-Decrease infusion rate by 6 units/kg/hour after 2 hours
-STAT aPTT/TEG 2 hours after rate change
**If the anti-Xa AND TEG do not agree, contact investigator and defer to anti-Xa nomogram for treatment

TEG anticoagulant parameters based upon:
48. Schears GA. Personal Communication from Dr. Greg Schears from Mayo Clinic from retrospective data analysis. 2014; November.

In addition to using the anti-xa level per the CTICU heparin nomogram as detailed above, TEG will also be used to help manage the anticoagulation, based on kaolin TEG r-time and alpha angle. Goals are set as: TEG r-time between 15 and 20 minutes and TEG alpha angle between 30 and 50 degrees. Heparinase and kaolin TEGs will be drawn each time. The heparinase and kaolin TEGs drawn will be able to show a more complete picture of coagulation, in that the heparin effect will be removed (while a patient is receiving heparin for anticoagulation) and underlying coagulopathy can be treated if found. Further, kaolin TEGs, while patients are receiving heparin, will be used for further anticoagulation management, as discussed above.

NOTE: While the ACT is not used at our institution for guiding anticoagulation therapy, many hospitals use this as the only anticoagulation guide. Thus, it would be appropriate to compare anti-xa as well as TEG to the ACT for the gathering of further data. Each time an anti-xa and TEG is drawn per the protocol, an ACT will also be drawn for study purposes.

Transfusion Parameters:

Hematocrit <22.5% or Hemoglobin <7.5 g/dl transfuse 2 units PRBC and recheck CBC

Platelet Count <100,000/ul or heparinase TEG MA <50 mm transfuse 1 dose of platelets

Signs of bleeding and heparinase TEG r-time >20 mm and an INR > 2.0 with clinical signs of bleeding transfuse 4 units of FFP

Signs of bleeding and Fibrinogen <180 mg/dl and heparinase TEG angle less than 30 mm 1 dose cryopercipiate (4units = 2.0 grams fibrinogen)

TEG transfusion parameters based upon:

48. Schears GA. Personal Communication from Dr. Greg Schears from Mayo Clinic from retrospective data analysis. 2014; November.

44. Shore-Lesserson L, Manspeizer H, DePerio M, et al (1999) Thromboelastography-Guided Transfusion Algorithm Reduces Transfusions in Complex Cardiac Surgery. Anesth Analg 88, 312-19.

The following parameters will specifically be investigated/recorded:

- Patient characteristics (sex, age, indication for ECMO, VV or AV ECMO, cannulation sites)
- Chest tube output and overall estimated blood loss
- Pre-ECMO/Pre-operative anticoagulation, including heparin, low molecular weight heparin, and other anti-aggregants including cyclooxygenase inhibitors such as aspirin, adenosine diphosphate receptor inhibitors such as clopidogrel, Glycoprotein IIB/IIIA (GpIIb/IIIa) inhibitors, phosphodiesterase inhibitors, adenosine reuptake inhibitors, and thromboxane inhibitors.
- Number of transfusions required while on ECMO (primary outcome)
- Time between transfusions
- Type of products transfused
- Pump exchanges required
- Oxygenator exchanges
- Occurrence of pump circuit clotting and clots in the oxygenator (visible clot which did not require circuit/pump exchange)
- Time to weaning from/removal of ECMO
- Need for surgical intervention for hemorrhage
- Occurrence of clinical thrombotic or hemorrhagic event (stroke for example)
- Specimen turn-around time for standard labs tests (CBC, ACT, PT, PTT, anti-Xa, INR, platelet count) and TEG results

Data will be collected for each enrolled patient until they are discontinued from ECMO.

2. Upload a copy of all materials used to collect data about subjects: (Attach all surveys, interview/focus group scripts, and data collection forms except for case report forms, SCID or KSADS):

Document	Category	Date Modified	Document History
There are no items to display			

3. * **Will blood samples be obtained for research purposes?**

● **Yes** ○ No

* **Provide the volume per withdrawal, total volume and frequency, and qualifications of individual performing the procedure:**

Blood drawn from the patient will come out of a pre-existing arterial line and will include a 1.0 ml syringe every 2-6 hours, depending on the value of the previous TEG and other standard of care tests (arterial blood gas, complete blood count, fibrinogen, platelet count, anti-xa). Patients will have on average 15 TEGs drawn over the course of the trial, for a total of 15ml of blood drawn for this study.

Consent Process

Enter N/A in response to the following questions if a Waiver of Consent is requested for all research activities or if no subjects are being enrolled.

1. * **Indicate where the consent process will take place and at what point consent will be obtained:**
The informed consent process will take place in the hospital pre-operative area prior to performing any of the research interventions/interactions.

2. * **Describe the steps that will be taken to minimize coercion and undue influence, including assurance that there is sufficient time for subjects to make an informed decision:**
In order to minimize the possibility of coercion or undue influence, the patients will be first informed that the choice of participation in the study is totally voluntarily in nature, and they will receive the standard of care when they decide not to participate in the study. Prospective patients will be encouraged to ask questions and to discuss the study with others during the consent process.

3. **For studies that involve multiple visits, describe the process to ensure ongoing consent:**
Not applicable

4. * **Steps to be taken to ensure the subjects' understanding:**
The physician investigator will have a discussion about the possibility of being a study participant with the patient/proxy several days to several hours prior to the surgery. The risk, benefits and goals of the study will be presented to the patient. On the day of the surgery, prior to any study procedures, if the patient is agreeable to participation in the study, the patient will sign consent to participate in the study.

   If the patient is unconscious, the physicians will review medical record for responsiveness and will consult with one another to determine patient is truly not able to provide consent. In this instance, a proxy will be approached to provide consent.

5. * **Are you requesting an exception to the IRB policy related to the informed consent process:**
   ○ Yes ● **No**

Since participants with impaired decision-making capacity to consent will be enrolled, address the following questions:

* **Describe the process for identifying the appropriate person to act as proxy for the participant:**
The research staff will look to see who signs the surgical and anesthesia consent on the patient's behalf. The Principal Investigator will then take jurisdiction to ensure that person is in fact the patient's legally authorized representative.

If a Legally Authorized Representative already exists for the patient, study

investigators will confirm legality of the proxy and approach that person for consent. If no LAR is named, study investigators will seek informed consent from the following individuals, in this order: natural or adoptive parent; adult child; adult brother or sister; any other available adult relative related through blood or marriage known and documented to have made decisions for the subject in prior health care settings etc.

*** Will assent be obtained from the participant who has impaired decision-making capacity?**

○ Yes ● **No**

*** Justify why their assent will not be sought:**

If a patient is cognitively available to give assent, then they also would be able to give informed consent and so obtaining assent would not be necessary

Consent Forms

1. **Consent Forms:**

	Document	Category	Date Modified	Document History
View	Consent Form(0.01)	Consent Form	8/22/2019	History

Refer to the following templates and instructional documents:

- Guidance - Consent Wording
- Template - Consent Document - Short Form
- HRP-090 - SOP - Informed Consent Process for Research
- HRP-091 - SOP - Written Documentation of Consent

Waiver/Alteration of Consent

1. * **Select all options that apply to the request to waive the requirement to obtain informed consent:**
Review of identifiable medical records

> *General Requirements: The Federal Policy (45 CFR 46.116 (d)) as well as guidance issued by the FDA requires the following criteria to be met for a waiver or alteration of consent to be approved with one exception.The FDA does not include a biospecimen provision (Item #4 below). You **MUST** provide a justification addressing how **each of the criterion are met for each option chosen** in Item #1.*

2. * **The research involves no more than minimal risk to the subjects;**
To enroll patients into the study, medical records of potential subjects will be reviewed. The medical record will be reviewed and if the patient is eligible, further consent process will be followed. If the patient is not eligible, patient's data will not be stored in the study database except the number of patients screened will be entered and stored within the UPMC firewall in a password protected file and drive

3. * **The waiver or alteration will not adversely affect the rights and welfare of the subjects;**
Medical record review and further eligibility into the study will not affect the patient's right to any standard therapy and welfare of subjects in anyway. If the patient is not eligible, they will receive standard perioperative therapy by anesthesia/ surgery and patient care team. Dr. Esper and other anesthesia team members of the study may provide anesthesia/surgical care/ECMO even if the patient's are ineligible for the study and follow the standard of care

4. **If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format (enter N/A for FDA regulated studies);**
Identification of potential subjects can be done by speaking with all potential subjects or by selectively identifying potentially eligible patients through medical record review. Medical record review will avoid speaking with all patients who may or may not require ECMO after their surgery. But any medical record review by a physician not directly involved in the patient care requires waiver of consent, Without this waiver, we cannot identify potential research subjects

5. * **The research could not practicably be carried out without the waiver or alteration;**
We cannot feasibility approach every patient who is having surgery without determining if they qualify beforehand.

6. * **Whenever appropriate, the subjects will be provided with additional pertinent information after participation;**
We will not acquire any information that will be pertinent to the participant's care

since this Waiver only applies to the this limited recruitment procedure. Only eligibility criteria (inclusion and exclusion criteria) of the patients will be reviewed. No other personnel or individual patient care information will be reviewed

7. * **Under what circumstances (if any) will you obtain consent from some of these subjects:**
A preliminary and limited assessment of patients medical charts will occur just to exclude patients with clear and certain exclusion criteria. Medical records will be reviewed under a waiver of consent for all subjects. They will provide informed consent prior to enrolling in the study.

Medical Records

1. You are required to submit this study to the Research Informatics Office, Health Record Research Request (R3). Per UPMC Policy HS-RS0005, all research projects that access or involve UPMC electronic protected health information (e-PHI) must be submitted to R3, with the exception of clinical trials that are contracted through the UPMC Office of Sponsored Programs and Research Support (OSPARS).

   Complete the R3 intake form available at http://rio.pitt.edu/services. An R3 representative will conduct a review. You will be notified once your R3 review is complete or if anything further is needed.

*** Describe the protected health information that will be collected from the covered entity and/or the research derived information that will be placed into the medical records:**

Patient characteristics (sex, age, indication for ECMO, VV or AV ECMO, cannulation sites), chest tube output and overall blood loss, Pre-ECMO anticoagulant drug therapies, number of transfusions required while on ECMO, time between transfusions, type of products transfused, pump exchanges required, oxygenator exchanges, occurrence of pump circuit clotting and clots in the oxygenator, time to weaning from/removal of ECMO, need for surgical intervention of hemorrhage, occurrence of clinical thrombotic or hemorrhagic event, specimen turn-around time for standard labs (CBC, ACT, PT, PTT, anti-Xa, INR, platelet count) and TEG result will be collected from the time patient is enrolled in the trial until ECMO is discontinued.

Electronic Data Management

1. * **Will only anonymous data be collected (select NO if identifiers will be recorded at anytime during the conduct of the study)?**

○ Yes ● No

Select all identifiers to be collected during any phase of the research including screening:

Name:	☑	**Internet Protocol (IP) Address:**	☐
E-mail address:	☐	**Web Universal Resource Locators (URLs):**	☐
Social security #:	☐	**Social security # (for Vincent payment only):**	☐
Phone/Fax #:	☐	**Full face photo images or comparable images:**	☐
Account #:	☐	**Health plan beneficiary #:**	☐
Medical record #:	☑	**Device identifiers/serial numbers:**	☐
Certificate/license #:	☐	**Vehicle identifiers/serial #/license plate #:**	☐
		Biometric identifiers, finger and voice prints:	☐

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* **a: Will you be collecting any of the following location data: geographic subdivisions smaller than a State such as street address, city, county, precinct, zip, geocodes, etc.?** ○ Yes ● No

* **b: Will you be collecting any date information such as birth date, death, admission, discharge, date of surgery/service?** ● Yes ○ No

c: List any other unique identifying numbers, characteristics or codes related to an individual that are to be collected:

d: Will you be collecting any data subject to the General Data Protection Regulation (GDPR)? ○ Yes ○ No

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* **For ALL identifiable data collected, will you be coding the data by removing the identifiers and assigning a unique study ID/code to protect the identity of the participant?** ● Yes ○ No

* **Will the data be HIPAA de-identified?** ● Yes ○ No

* **Briefly describe your plan to store coded data separately from the identifiable data:**	Identifiable data will be kept in a single encrypted file on the shared (z:) drive behind the UPMC firewall. All other study-related data (such as paper records and data for analysis) will have all identifiers removed. To protect against the possibility of breach of confidentiality, all data collected will be identifiable only by an unique subject ID number, and no personal identifiers will be stored with the data. Linkage files identifying subjects will be stored only in the UPMC server and will be linked to the physical record with a subject code. Physical records will be kept in locked files accessible only by study staff; electronic data will be handled and protected as described above on the UPMC server.

2. **During this study, will restricted data as defined by the University's Data Risk Classification matrix (** https://www.technology.pitt.edu/security/data-risk-classification-and-compliance **) be processed, stored, or transmitted?**

○ Yes ○ No

3. * **During this study, will sensitive data (**https://www.hrpo.pitt.edu/electronic-data-security**) be collected where disclosure of identifying information could have adverse consequences for subjects or damage their financial standing, employability, insurability, educational advancement, reputation or place them at risk for criminal or civil liability?**

● **Yes** ○ No

4. * **Select all locations where data will be stored or archived(including e.g.,** personal / employer laptop or desktop**): If you have access to University owned or controlled resources, facilities, or repositories, such as computer servers, please choose that option to comply with the** Research Data Management Interim Policy R1 14**.**

Please note that to address Research Security Requirements, University data must be stored in University owned, controlled, or approved repositories, such as Pitt OneDrive. If UPMC or external electronic repositories must be used, they must be approved by Pitt IT.

	Storage Device	Description	Identifiable Data	Sensitive Data	De-Identified/Anonymous Data
View	UPMC: Departmental or Hospital Server		yes	yes	yes
View	UPMC owned desktop, laptop or other device		no	no	no

5. * **Select all technologies being used to collect data or interact with subjects: Technologies selected in this section may require a Vendor Security**

Risk Assessment, which can be requested here.

N/A

Data Safety and Monitoring

1. * **Describe your plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe. The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor:**
   The following data and safety monitoring plan will be instituted to ensure the safety of the subjects and to maintain the confidentiality of the research data. The principal investigator, co-investigators and study coordinators will perform monthly or quarterly reviews of the accrued data and incidence of adverse effects to ensure validity and integrity of the data and to reassess the benefit-to-risk ratio on a frequent and regular basis. Subject privacy and research data confidentiality will be ensured by reviewing the adequacy of the secure location of where the data is stored and by making sure it is all de-identified with the coded case numbers as described previously. Adverse events, data quality and timeliness of participant recruitment will all be reviewed with the team of investigators, who will determine whether the study should be continued as planned, changed or terminated.

2. * **Describe your plan for sharing data and/or specimens:**
   No data sharing is planned.

3. **If any research data is collected, stored, or shared in a paper format, address what precautions will be used to maintain the confidentiality of the data:**
   Paper-based records will be kept in a secure location, computer-based files will be available to personnel involved in the study through access privilege, whenever possible identifiers will be removed from study-related information, patients' computer medical information will only be available through password access.

Risk and Benefits

1. * Enter all reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to subjects' participation in the research:

View

Research Activity	**Review of Medical Records**
Common Risks	***No Value Entered***
Infrequent Risks	***No Value Entered***
Other Risks	**Breach of confidentiality.**

View

Research Activity	**Blood Draw From Arterial Line**
Common Risks	***No Value Entered***
Infrequent Risks	***No Value Entered***
Other Risks	***No Value Entered***

View

Research Activity	**TEG Interpretation**
Common Risks	***No Value Entered***
Infrequent Risks	***No Value Entered***
Other Risks	**It is possible that incorrect interpretation of TEG results could lead to mismanagement of coagulation therapy.**

2. * Describe the steps that will be taken to prevent or to minimize risks:

All investigators who will access the identifiable medical records already have normal clinical access to all necessary records, as granted by the privacy office for job-related needs. Thus, only HIPAA trained research staff will be handling this information and this information will be stored in a locked database protected by the UPMC firewall. Additionally, all data generated under this protocol will be monitored and maintained by the principal investigator. Any databases that contain identifiable information will be stored on a departmental drive on the UPMC network created for the principal investigator, and all data will be deidentified according to the HIPPA "safe harbor" guidelines prior to statistical analysis.

In order to avoid coagulation mismanagement as the result of a misinterpreted TEG result, traditional standard of care coagulation testing will also be done (anti-Xa, ACT) in conjunction with the TEG and will be the driving force in coagulation management.

Arterial line blood draws will be limited to the lowest number possible based on previous TEG and conventional test values. The average patient will have a maximum of 15 blood draws over the duration of the trial.

3. **Financial risks - will the subject or insurer be charged for any research required procedures?**

● **Yes** ○ No

* **Address each procedure with a justification and indicate if charges are incurred for investigational drugs/devices. Address, if applicable, a contingency plan for those not able to cover the cost of participation:**
Charges will be billed only for procedures performed as part of the subject's routine clinical care.

4. **Describe the steps that will be taken to protect subjects' privacy:**
Research intervention will be conducted in a private room with the patient, collected information will be limited to that which is necessary for the goals of the research study, access to the patient's private information will be limited to those involved in the patient's medical care.

5. **What steps will be taken in the event that a clinically significant, unexpected disease or condition is identified during the conduct of the study:**
The patient's primary medical team will be immediately notified of the unexpected, clinically significant condition. The patient's clinically significant medical condition will be managed accordingly. If any of the clinically significant medical condition is related to the study, then the patient's participation in the study will be re-evaluated, with the possibility of the patient being withdrawn from the study if this leads to the resolution of the clinically significant medical condition.

6. **Describe the potential benefit that individual subjects may experience from taking part in the research or indicate if there is no direct benefit. Do not include benefits to society or others:**
There is no direct benefit to the subjects.

7. **Do you anticipate any circumstances under which subjects might be withdrawn from the research without their consent?**

○ Yes ● **No**

8. **Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection and data already collected:**
After withdrawing from the study, each subject's data will be kept for the required data retention period in a secure, locked facility, and will be destroyed after that period. Patients' data might be used for data analysis if deemed necessary/useful (e.g. reason of withdrawal).

Conflict of Interest

Institutional Financial Interests

1. * **To the best of your knowledge, has the University of Pittsburgh optioned or licensed technology that will be tested or evaluated in this research?**
   - ○ Yes ○ No

Ancillary Reviews

1. **Ancillary reviews or notifications selected below are required based on previous answers to questions. If a selection is incorrect, return to the appropriate page and adjust the answers to questions on that page:**

- [ ] Conflict of Interest (**COI**)
- [ ] Clinical and Translational Research Center (**CTRC**)
- [ ] Data Security
- [ ] Honest Broker
- [ ] UPMC Investigational Drug Service
- [ ] Pitt Medical School Review
- [ ] Pitt+Me
- [ ] IND & IDE Support(**IIS**)
- [ ] Radioactive Drug Research Committee (**RDRC**)(study involves the evaluation or use of procedures that emit ionizing radiation)
- [ ] ORP Business **Manager** (required for industry sponsored studies)
- [ ] Religious Directives
- [x] Scientific Review
- [x] Health Record Research Request (**R3**) (required if using UPMC clinical data and authorization for other UPMC data sources for research)
- [x] UPMC Office of Sponsored Programs and Research **Support** (using UPMC facilities and/or UPMC patients during the conduct of the study)

2. **Additional ancillary reviews the PI may choose to include as needed for the research:**

- [ ] Human Stem Cell Oversight (**hSCRO**)
- [ ] Institutional Biosafety Committee (**IBC**)(study involves deliberate transfer of recombinant or synthetic nucleic acid molecules)

Good Clinical Practice (GCP) Training

1. * **Regardless of funding source, is this study a clinical trial (**as defined by the NIH**)?**
   - ● **Yes** ○ No

ClinicalTrials.gov Information

Visit the University of Pittsburgh Office for ClinicalTrials.gov website or contact ctgov@pitt.edu for further information.

2. * **Was this study registered, or will it be registered, on ClinicalTrials.gov?**
   - ● **Yes** ○ No

3. * **Is the University of Pittsburgh or UPMC the Sponsor Organization for this study record?**
   - ● **Yes** ○ No

   * **Who will be the Responsible Party for this study record?**

   Principal Investigator of this IRB application

Supporting Documents

1. **Attach any additional supporting documents not previously uploaded. Name the documents as you want them to appear in the approval letter:**

	Document	Category	Date Modified	Document History
View	Esper ECMO references(0.01)	Other	8/22/2019	History

Add Storage Information

1. * **Select a Storage Type:**
   UPMC: Departmental or Hospital Server

2. **Description:**

3. * **Will identifiable data be stored in this location?**
   ● **Yes** ○ No

4. * **Will sensitive data be stored in this location?**
   ● **Yes** ○ No

5. **Will de-Identified or anonymous data be stored in this location?**
   ● **Yes** ○ No

6. **Provide additional information as needed:**

Add Storage Information

1. * **Select a Storage Type:**
   UPMC owned desktop, laptop or other device

2. **Description:**

3. * **Will identifiable data be stored in this location?**
   ○ Yes ● **No**

4. * **Will sensitive data be stored in this location?**
   ○ Yes ● **No**

5. **Will de-Identified or anonymous data be stored in this location?**
   ○ Yes ● **No**

6. * **Is anti-virus software installed and up to date on all devices and are the operating systems kept up-to-date on all devices?**
   ● **Yes** ○ No

7. **Provide additional information as needed:**

View: Pitt Risk

Risk

1. * **Research Activity:**
   Review of Medical Records

2. **Common Risks:**

3. **Infrequent Risks:**

4. **Other Risks:**
   Breach of confidentiality.

View: Pitt Risk

Risk

1. * **Research Activity:**
   Blood Draw From Arterial Line

2. **Common Risks:**

3. **Infrequent Risks:**

4. **Other Risks:**

View: Pitt Risk

Risk

1. * **Research Activity:**
   TEG Interpretation

2. **Common Risks:**

3. **Infrequent Risks:**

4. **Other Risks:**
   It is possible that incorrect interpretation of TEG results could lead to mismanagement of coagulation therapy.