December 20, 2017

Application to Join the PETAL Network as a New Site for the CLOVERS Trial

I. Cover Letter

Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network

Re: Call for applications to join the NHLBI PETAL Network

Dear Emergency Medicine and Critical Care Investigators:

The Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network is seeking applications for institutions to join the network as new enrolling sites. This document contains instructions on how to submit an application to join the network.

The PETAL Network is funded by the National Heart Lung and Blood Institute (NHLBI) to conduct clinical trials to advance the prevention and treatment of acute lung injury. The network is organized in a hub-and-spoke model with 12 Clinical Centers serving as the administrative hubs. Each Clinical Center is an academic medical center in the United States and is affiliated with 2-5 other U.S. hospitals that serve as enrolling sites (spokes).

Ongoing trials in the PETAL Network include:
(1) Re-evaluation of Systemic Early Neuromuscular Blockade (ROSE): NCT02509078
(2) Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET): NCT03096314

In 2018, PETAL will launch a new trial, entitled Crystalloid Liberal or Vasopressor Early Resuscitation in Sepsis (CLOVERS). In order to meet enrollment goals, PETAL is seeking additional enrolling sites (spokes) to join the network for the CLOVERS trial. A summary of the CLOVERS trial protocol is included in this packet. The full CLOVERS protocol and case report form are available upon request from Nancy Ringwood (NRINGWOOD@mgh.harvard.edu).

The primary goal of additional sites is to enroll patients in CLOVERS. Enrollment in CLOVERS will require early identification and randomization of adults with septic shock. Applying institutions need to identify two investigators—one who will lead CLOVERS in the emergency department and one who will lead the trial after admission to the intensive care unit. Institutions with experience in acute care and critical care trials requiring early enrollment within 6-12 hours of hospital presentation are especially encouraged to apply.

Interested investigators are encouraged to contact us to discuss preparation of an application.

Sincerely,

The PETAL Network Investigators

CLOVERS Expansion Committee for the PETAL Network

Wesley Self (wesley.self@vanderbilt.edu) Michelle Gong (MGONG@montefiore.org)

Roy Brower, Colin Grissom, Duncan Hite, Tracy Holloway, Robert Hyzy, Michael Matthay, Chad Miller, Marc Moss, Lora Reineck, Nancy Ringwood, Jay Steingrub, Thomas Terndrup, B. Taylor Thompson, Donald Yealy

II. PETAL Network Description

Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network

PETAL Network website: petalnet.org

Funding Organization: National Heart Lung and Blood Institute (NHLBI) (PO: Lora Reineck, MD)

Clinical Coordinating Center: Massachusetts General Hospital (PI: David A. Schoenfeld, PhD)

Current Funding Cycle: June 2014 – April 2021

The purpose of the PETAL Network is to develop and conduct randomized controlled clinical trials to prevent or treat, and/or improve the outcome of patients who have, or who are at risk for, Acute Lung Injury (ALI) or Acute Respiratory Distress Syndrome (ARDS).

The PETAL Clinical Coordinating Center is Massachusetts General Hospital. The PETAL network is organized in a hub-and-spoke model with 12 Clinical Centers serving as the administrative hubs. Each Clinical Center is an academic medical center in the United States and is affiliated with 2-5 other U.S. hospitals that serve as enrolling sites (spokes). A list of Clinical Centers is included below in the application.

In 2018, the PETAL Network will launch a new trial entitled, Crystalloid Liberal or Vasopressor Early Resuscitation in Sepsis (CLOVERS) (Protocol Chair: Nathan Shapiro, MD, MPH, Beth Israel Deaconess Medical Center; Co-chair: Ivor Douglas, MD, Denver Health Medical Center). The PETAL Network is seeking additional enrolling sites (spokes) to join existing Clinical Centers (hubs) to enroll in the CLOVERS trial. Information about the PETAL Network for potential new sites is outlined here.

1. Affiliation with a Clinical Center

Each site added to the network will be affiliated with one of the existing PETAL Clinical Centers. During the application process, each site must identify a Clinical Center to sponsor the application. Each Clinical Center will be allowed to add a maximum of one additional site through this mechanism. Multiple sites can name the same Clinical Center during the application process. If one Clinical Center is affiliated with more than one site that is recommended for entry into the Network, the CLOVERS Expansion Committee will work with the Clinical Center and sites to attempt to reassign new sites to other Clinical Centers.

2. Contracts

After joining the network, a new site will receive separate contracts for each trial in which it will participate. Contracts will be issued from the Clinical Coordinating Center to the affiliated Clinical Center. A sub-contract will then be issued from the Clinical Center to the new site.

3. Payment

Each enrolled patient in the CLOVERS trial will result in payment of $4,729.15 (inclusive of indirects) from the Clinical Coordinating Center to the Clinical Center. A plan for payment to the enrolling site should be mutually agreed upon by the enrolling site and affiliated Clinical Center. The Network suggests that the Clinical Center retain 5% of the payment for each enrolled patient to cover monitoring and administrative responsibilities.

4. Central IRB (cIRB)
The PETAL Network uses a cIRB housed at Vanderbilt University for all trials. In order to join the network, sites must commit to using the cIRB. As part of the application to join the network, sites should submit a letter from a leader within their local IRB stating the local IRB will cooperate with the cIRB for PETAL trials.

5. Expectations for CLOVERS enrollment
Sites added to the PETAL Network for the CLOVERS trial are expected to enroll an average of at least 24 patients per year (2 patients per month).

6. Data Entry
Data are entered into the electronic data capture system StudyTRAX. Data are expected to be entered by the following time points: (1) Screening and baseline data entered by study day 30; (2) All remaining data entered by study day 60.

7. Monitoring
Affiliated Clinical Centers for each new site will be responsible for monitoring trial execution and data quality at the site. A monitoring plan should be mutually agreed upon by the new site and affiliated Clinical Center and summarized in the application.

8. Participation in Other PETAL Trials
The primary goal of adding new sites to the Network is to enhance enrollment in CLOVERS. After new sites have established a strong record of enrollment in CLOVERS, they will be encouraged to apply to the PETAL Institutional Support Committee to join other PETAL trials. Enrollment in CLOVERS will be one of the criteria used to evaluate applications to join additional trials.

III. CLOVERS Trial Summary

1. Title

Crystalloids **L**iberal **O**r **V**asopressors **E**arly **R**esuscitation in **S**epsis **(CLOVERS)**

2. Objective

Primary Objective: To determine the impact of a restrictive fluids strategy (vasopressors first followed by rescue fluids) as compared to a liberal fluid strategy (fluids first followed by rescue vasopressors) on 90-day in-hospital mortality in patients with sepsis-induced hypotension.

3. Hypothesis

Primary Hypothesis: Restrictive (vs liberal) fluid treatment strategy during the first 24 hours of resuscitation for sepsis-induced hypotension will reduce 90-day in-hospital mortality.

4. Study Design

Study Design: Multicenter, prospective, phase 3 randomized non-blinded interventional trial of fluid treatment strategies in the first 24 hours for patients with sepsis-induced hypotension.

1. We will emphasize early screening and protocol initiation, and enroll a maximum of 2320 patients with suspected sepsis-induced hypotension.
   - ✓ All patients will receive at least 1 liter of fluids prior to meeting study inclusion criteria (and no more than 3 liters prior to randomization).
   - ✓ Patients will be enrolled within 4 hours of meeting study inclusion criteria
   - ✓ Any type of isotonic crystalloid (normal saline, ringers lactate, or a balanced solution such as plasmalyte) is permitted.

2. Restrictive Fluids (Early Vasopressors) Group (See Protocol Schema Appendix A)
   - ✓ Norepinephrine will be used as preferred vasopressor and titrated to achieve mean arterial pressure (MAP) between 65 mmHg and 75 mmHg
   - ✓ “Rescue fluids” may be administered as 500ml boluses if predefined rescue criteria are met

3. Liberal Fluids (Fluids First) Group (See Protocol Schema Appendix A)
   - ✓ Additional 2 liter intravenous fluid bolus upon enrollment
   - ✓ Administer 500ml fluid boluses for fluid triggers until 5 liters administered or development of clinical signs of acute volume overload develop
   - ✓ “Rescue vasopressors” may be administered after 5 liters of fluid, for development of acute volume overload, or if other predefined rescue criteria are met

4. Other care
   - ✓ Other elements of care (e.g. antibiotics, ventilation strategies, etc.) will be recommended to reflect current “best-practice” where feasible and appropriate

5. Inclusion Criteria

1. A suspected or confirmed infection (broadly defined as administration or planned administration of antibiotics)
2. Sepsis-induced hypotension defined as systolic blood pressure < 100 mmHg or MAP < 65 mmHg after a minimum of at least 1 liter of fluid (*Fluids inclusive of pre-hospital fluids; blood pressure must be below any known or reported pre-morbid baseline).

6. Exclusion Criteria

1. Age < 18 years
2. More than 4 hours elapsed since meeting inclusion criteria or 24 hours elapsed since admission to the hospital
3. Patient already received 3 liters of intravenous fluid (includes prehospital volumes)
4. Unable to obtain informed consent
5. Known pregnancy
6. Hypotension suspected to be due to non-sepsis cause (e.g. hemorrhagic shock)
7. Blood pressure is at known or reported baseline level
8. Severe Volume Depletion from an acute condition other than sepsis.
   In the judgment of the treating physician, the patient has an acute condition other than sepsis causing (or indicative) of *severe volume depletion;
   Examples include: Diabetic ketoacidosis, high volume vomiting or diarrhea, hypersomolar hyperglycemic state, and nonexertional hyperthermia (heat stroke); severe is defined by the need for substantial intravenous fluid administration as part of routine clinical care
9. Pulmonary edema or clinical signs of new fluid overload (e.g. bilateral crackles, new oxygen requirement, new peripheral edema, fluid overload on chest x-ray)
10. Treating physician unwilling to give additional fluids as directed by the liberal protocol
11. Treating physician unwilling to use vasopressors as directed by the restrictive protocol.
12. Current or imminent decision to withhold most/all life-sustaining treatment; this **does not** exclude those patients committed to full support except cardiopulmonary resuscitation
13. Immediate surgical intervention planned such that study procedures could not be followed
14. Prior enrollment in this study

7. Randomization and Initiation Time Window

All patients must be enrolled and randomized within 4 hours of meeting inclusion criteria. Patients may become eligible in the ED, hospital ward, or ICU.

8. Primary Endpoint

The primary outcome is all-cause mortality prior to discharge home before day 90.

9. Secondary Endpoints

1. 28-day organ support free days (alive and without mechanical ventilation, new renal replacement or vasopressors; vasopressors prior to 48 hours excluded)
2. 28-day ventilator free days
3. 28-day renal replacement free days (new renal replacement therapy)

4. 28-day vasopressor free days (vasopressors prior to 48 hours excluded)
5. 28-day ICU free days
6. 28-day hospital free days
7. Initiation of mechanical ventilation
8. Initiation of renal replacement therapy
9. Change in creatinine-based KDIGO stage between baseline and 72 hours
10. Change in SOFA score between baseline and 72 hours
11. 90-day all-cause mortality
12. Development of ARDS within 7 days
13. New onset atrial or ventricular arrhythmia

10. Process of Care Metrics

Process of Care Metrics: We will assess whether the proposed intervention has effectively altered care as intended by measuring:

- ✓ Total intravenous fluids administered over initial 6 hours
- ✓ Total intravenous fluids administered over initial 24 hours
- ✓ Proportion receiving vasopressors and timing of vasopressor initiation within 24-hour study period
- ✓ Total fluids administered prior to initiation of vasopressors

11. Sample Size/Interim Monitoring

1. Randomization 1:1; two-sided alpha 0.05.
   A total of 2320 patients are needed to detect a 4.5% absolute mortality difference between treatment groups with 90% power assuming 15% mortality in the liberal fluids group. The principal analysis will be intent-to-treat, based upon randomization assignment.
2. There will be a protocol feasibility assessment phase at the 100-, 200-, and 300- patient marks. Aggregate data blinded to outcomes will be used to assess patient accrual, treatment protocol compliance, and separation of intravenous fluid and/or vasopressor administration. Protocol adjustments may be made at the 100-, 200-, and 300- patient marks to optimize the protocol. The study may be halted during the feasibility assessment phase for failure to meet pre-specified stopping guidelines.
3. Trial progress will be evaluated by an independent Data and Safety Monitoring Board (DSMB) to determine whether the study should stop for superiority of either the liberal or restrictive fluid strategies; or, for projected trial futility. (See Appendix B) There will be two interim analyses and a final analysis conducted when approximately each successive 1/3 of the patients have been enrolled.

IV. Application Instructions

Due Date for Application:
March 1, 2018

Mechanism for Submitting Application:
Please submit a single document responding to each section outlined below. The document should be no longer than 8 pages (biosketches are not included in these page limits). Email the document to the following 2 people:

Cathryn Oldmixon COLDMIXON@mgh.harvard.edu
Nancy Ringwood NRINGWOOD@mgh.harvard.edu

1. Contact Information

Please provide the name and contact information for the corresponding investigator for your application.

2. Affiliation with a PETAL Clinical Center

New enrolling sites (spokes) must be affiliated with one of the existing PETAL Clinical Centers (hubs). Please identify the affiliated Clinical Center for your application. Include a letter of support from the principal investigators of your affiliated Clinical Center. Clinical Centers interested in adding a new site are listed in the Table below. Before you prepare your application, we recommend identifying a clinical center affiliation. You are encouraged to contact investigators listed below to discuss potential affiliation.

PETAL Clinical Centers Seeking New Sites for CLOVERS		
Clinical Center	**Investigators**	**Investigator Contact (email)**
ALIGNE (Baystate Medical Center)	Jay Steingrub Peter Hou	jay.steingrub@baystatehealth.org
Boston (Beth Israel Deaconess)	Danny Talmor Nate Shapiro	nshapiro@bidmc.harvard.edu
California (UCSF)	Michael Matthay Greg Hendey	michael.matthay@ucsf.edu
Colorado (University of Colorado)	Marc Moss Adit Ginde	marc.moss@ucdenver.edu adit.ginde@ucdenver.edu
Michigan (University of Michigan)	Bob Hyzy Pauline Park	rhyzy@umich.edu
Montefiore (Montefiore Medical Center)	Michelle Gong Lynne Richardson	mgong@montefiore.org
Pacific Northwest (University of Washington)	Terri Hough Bryce Robinson	cterrlee@uw.edu
Pittsburgh (University of Pittsburgh)	Don Yealy Derek Angus	yealydm@upmc.edu
Southeast (Wake Forest University)	Chad Miller Clark Files	cmiller@wakehealth.edu dfiles@wakehealth.edu
Utah (Intermountain Medical Center)	Colin Grissom Joey Bledsoe	colin.grissom@imail.org
Vanderbilt (Vanderbilt University)	Todd Rice Wesley Self	wesley.self@vanderbilt.edu

3. Institution and Personnel

Please describe the following:

A. The hospital(s) where patients will be enrolled into CLOVERS.
B. The emergency department(s) and intensive care unit(s) where patients enrolled in CLOVERS will be managed.
C. The investigator who will lead CLOVERS in the ICU.
D. The investigator who will lead CLOVERS in the ED.
E. Current research infrastructure, including staffing in the ED and ICU, and hours of coverage for research activities (e.g. screening).
F. The research team that will conduct CLOVERS, including screening, enrollment, protocol execution, and data entry.

Please include relevant clinical research experience, especially experience in trials requiring early enrollment and trials enrolling septic patients.

4. Commitment to Central IRB

All PETAL trials utilize a central institutional review board (cIRB). A requirement for joining PETAL is commitment to using the cIRB. Please include a letter from a leader within the IRB at your institution stating your institution is committed to cooperating with the cIRB for PETAL trials. The PETAL cIRB is housed at Vanderbilt University and led by Dr. Todd Rice. Please direct any questions about the cIRB to Dr. Rice at todd.rice@vanderbilt.edu.

5. Execution of CLOVERS

Please describe how you plan to conduct CLOVERS at your institution. Specifically, describe:

A. Your plan for early screening and enrollment given CLOVERS requires enrollment within 4 hours of meeting inclusion criteria and before the patient receives >3 liters of IV fluid.
B. Plans for ensuring protocol compliance for the entire 24 hour protocol, and maintaining high quality data. This includes plans to ensure seamless transition of study patients from the ED to the ICU to ensure continuity and compliance with the protocol.
C. Please include an estimate for how many patients you anticipate enrolling in CLOVERS per month. What is the source of this estimate?

6. Current and Previous Clinical Trials Experience

A. Please provide a table outlining the clinic research experience of your group during the past 5 years. Use the table shell below. Indicate whether enrollment into the studies listed in the Table will occur concurrently with CLOVERS.
B. Sites in PETAL must affirm they prioritize enrollment into NIH clinical trials over enrollment into non-NIH studies. Please include this affirmation within your application.
C. If other studies will be ongoing during CLOVERS, please include a description of your strategy for the screening and enrolling into multiple clinical studies simultaneously.

Table shell to describe previous clinical research experience.								
Study (funding source)	Years of enrollment	Study type (e.g. RCT, cohort, ect)	General description of eligibility criteria	Trial intervention	Concurrent with CLOVERS (Y/N)	Potential overlap with CLOVERS eligibility (Y/N)	# patients enrolled at our site	Notes about enrollment at our site

7. Monitoring and Data Quality

Please describe your plan for ensuring high quality, accurate data and timely data entry. Your affiliated PETAL Clinical Center will be responsible for monitoring protocol compliance and data quality. Please describe a monitoring plan jointly developed between your site and your affiliated PETAL Clinical Center.

8. Biosketches

Please include biosketches for the two investigators who will lead CLOVERS at your site – one investigator who will lead CLOVERS in the emergency department and one who will lead CLOVERS in the ICU.

V. Application Review Process

Applications to join the PETAL Network as a new site for CLOVERS will be reviewed according to the following procedures. The review panel will score applications with the goal of selecting sites that have the greatest potential to successfully contribute to the CLOVERS trial with robust enrollment, strong adherence to the protocol, and high quality data.

1. Review Panel

Each application will be scored by a review panel consisting of Roy Brower (PETAL Steering Committee Chair), B. Taylor Thompson (PETAL Clinical Coordinating Center Clinical Director), and content experts from emergency medicine and critical care medicine. The content experts will not be affiliated with PETAL or any of the sites applying to join PETAL. These content experts will be selected by the CLOVERS Expansion Committee after site applications have been received.

2. Application Eligibility

In order for an application to be scored, it must: (1) identify a PETAL Clinical Center the new site will be affiliated with; (2) include a letter describing commitment from the local IRB to cooperate with the PETAL cIRB; and (3) identify two separate investigators, one who will be responsible for CLOVERS in the emergency department, and one who will be responsible for CLOVERS in the ICU.

3. Review Procedures

Each eligible application will be assigned a primary and secondary reviewer from the review panel. The primary and secondary reviewer will score the application independently. Then the primary and secondary reviewer will present the application to the entire review panel. Final scores will be determined by the full review panel at the time of discussion. Final scores will be used to rank sites. The review panel will present a rank list of applications along with associated scores and reviewer comments to the PETAL Steering Committee. The Steering Committee will then vote on which sites to add to the network.

Each Clinical Center will be allowed to add a maximum of one additional site through this mechanism. Multiple sites can name the same Clinical Center during the application process. If one Clinical Center is affiliated with more than one site that is recommended for entry into the Network, the CLOVERS Expansion Committee will work with the Clinical Center and sites to attempt to reassign new sites to other Clinical Centers.

4. Scoring Criteria

Following procedures outlined by NIH for scoring research grants, applications will be scored using a 9-point scale (1 exceptional; 2 outstanding; 3 excellent; 4 very good; 5 good; 6 satisfactory; 7 fair; 8 marginal; 9 poor).

A summary score for the entire application (overall score) will be provided as well as individual scores for each criterion listed in the score card below.

Score Card: Each criterion is scored with whole numbers 1 (exceptional) - 9 (poor).			
Criterion	**Reviewer #1**	**Reviewer #2**	**Panel (Final)**
Overall Score			
Investigators			
Research infrastructure			
Potential for robust CLOVERS enrollment			
Plan to execute CLOVERS with high protocol adherence			
Data quality and monitoring plan			
Rank List Number:			