DEPARTMENT OF HEALTH & HUMAN SERVICES

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September 28, 2020

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Director
Public Citizen's Health Research Group
1600 20th Street, NW
Washington, DC 20009

Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen's Health Research Group
1600 20th Street, NW
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RE: **Project Title:** Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis Trial
Funder: National Heart, Lung, and Blood Institute, National Institutes of Health
Principal Investigator: David A. Schoenfeld, Ph.D., Massachusetts General Hospital, Clinical Coordinating Center for the NHLBI-funded Clinical Trials Network for the Prevention and Early Treatment of Acute Lung Injury (PETAL Network)
ClinicalTrials.gov Identifier: NCT03434028

Dear Drs. Carome and Wolfe:

Thank you for contacting the Office for Human Research Protections (OHRP), Department of Health and Human Services (DHHS) (letter dated August 28, 2018), regarding Public Citizen's concerns about the Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) Trial.

Public Citizen alleged that this trial failed to "(a) materially comply with key requirements of Department of Health and Human Services (HHS) regulations for the protection of human subjects at 45 C.F.R. Part 46 and (b) satisfy the basic ethical principles upon which those regulations are founded." Specifically, Public Citizen alleged that based on its review of the protocol that was current at the time, the trial did not satisfy the following regulatory requirements: (1) the risks to the subjects are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk (45 CFR 46.111(a)(1)); and (2) the risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge expected to result (45 CFR 46.111(a)(2)). In addition, Public Citizen alleged that the sample consent form that it reviewed was deficient with regard to the following required elements of consent: (1) a description of the procedures to be followed and identification of any procedures that are experimental (45 CFR 46.116(a)(1)); and (2) a description of any reasonably foreseeable risks or discomforts to the subject (45 CFR 46.116(a)(2)).

According to Public Citizen's letter, the allegations that it raised about the trial and sample consent form were largely related to the following stated concern:

> . . . because the trial's design does not account for how current usual care varies based on the severity of sepsis with which subjects enrolling in the trial present, the two management strategies under investigation will lead to inappropriate or misaligned treatment for some subjects in each trial group. In randomized clinical trials like CLOVERS that enroll subjects with variable degrees of disease severity, misalignments can occur when subgroups of subjects are randomly assigned to receive levels of normally titrated therapeutic interventions that are inconsistent with their disease severity and significantly different from what they would have received outside of the clinical trial (page 2 of Public Citizen letter to OHRP).

Following from this expressed concern, Public Citizen alleged that neither arm of the protocol represents "usual care" for the treatment of patients with low blood pressure from sepsis and that subjects may receive medical care that is not appropriate for their condition, leading to worse outcomes than if they did not participate in the protocol. Public Citizen also alleged that the study results will not provide accurate guidance for future medical practice because the lack of a "usual care" arm means that data will not be collected comparing the two arms of the study to "usual care." In addition, Public Citizen alleged that the consent form does not explain to prospective subjects that neither arm of the protocol is "usual care."

Public Citizen's letter also indicates that, in assessing the CLOVERS trial, it sought expert advice from the Senior Investigator and Chief of the Anesthesia Section in the Critical Care Medicine Department at the National Institutes of Health (NIH) and the Senior Investigator and Head of the Critical Care Medicine Section in the Critical Care Medicine Department at the NIH Clinical Center. Both advisers are internationally recognized experts on the pathophysiology and treatment of sepsis and septic shock, critical care medicine, and the design and conduct of clinical trials in these areas.

CLOVERS Trial

CLOVERS is a multicenter, randomized, un-blinded, two-arm clinical trial to determine the impact of a restrictive fluids ("Medicine to Raise Blood Pressure First") strategy as compared with a liberal fluids ("Fluids First") strategy on 90-day in-hospital mortality. The trial seeks to enroll approximately 2,320 adult subjects who have sepsis-induced hypotension. It is funded by the National Heart, Lung and Blood Institute (NHLBI) and led by emergency medicine and critical care medicine experts from the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network. The PETAL Network is a network of twelve clinical centers and one clinical coordinating center competitively funded by the NHLBI after peer review to develop and conduct randomized controlled clinical trials to prevent Acute Respiratory Distress Syndrome (ARDS) or provide early treatment to improve the outcome of patients who have ARDS. The protocols are developed and approved by the PETAL steering committee, and then subsequently reviewed and approved by the protocol review committee and data and safety monitoring board, all of which include experts in sepsis, critical care, emergency medicine, and clinical trials.

The primary hypothesis is that restrictive (Medicine to Raise Blood Pressure First), as compared to liberal (Fluids First), fluid treatment during the first 24 hours of resuscitation for sepsis-induced hypotension will reduce 90 day in-hospital mortality. The scientific justification for the original CLOVERS study (prior to the revisions reflected in version VI of the protocol) was explained in Self WH, et al. Liberal Versus Restrictive Intravenous Fluid Therapy for Early Septic Shock: Rationale for a Randomized Trial. Ann Emerg Med 2018; 72:457-466. The introduction of that article summarizes the rationale by noting that:

> For the past two decades, clinicians in the emergency department (ED) and intensive care unit (ICU) have routinely administered large volumes of intravenous fluid (IVF) to patients with septic shock, often totaling greater than 5 liters (L) in the first several hours of resuscitation. However, an improved mechanistic understanding of potential harm from excessive fluid administration and emerging observational data associating positive fluid balance with higher mortality have recently challenged the paradigm of large-volume fluid resuscitation.
>
> With inadequate evidence to support a specific IVF strategy for the management of early septic shock, two alternative approaches have emerged: (1) a liberal fluids approach that relies on a larger volume of initial IVF administration [often 50 – 75 ml/kg (4–6 liters in an 80 kg adult)]; and (2) a restrictive fluids approach consisting of a smaller volume of initial IVF [often ≤30 ml/kg (≤2–3 liters)] and earlier use of vasopressors. Because of the equipoise surrounding these competing treatment strategies, we designed a randomized clinical trial to compare a liberal versus restrictive approach to IVF resuscitation—the Crystalloid Liberal or Vasopressor Early Resuscitation in Sepsis (CLOVERS) trial.

The article then goes on to discuss other studies that support the two approaches for the management of early septic shock.

OHRP Response

Due to the nature of the concerns outlined in Public Citizen's letter, OHRP obtained additional information from the experts in septic shock who had prepared the analysis of the CLOVERS study that accompanied the Public Citizen letter of August 28, 2018. At Public Citizen's request, on September 11, 2018, we met with Public Citizen and the two experts noted above to discuss these concerns. Afterwards, because of the complexities of the CLOVERS study and questions about its relationship to current practices in the treatment of sepsis, OHRP had additional conversations with the same two experts, and with other experts in the field, to discuss the issues raised in Public Citizen's letter.

OHRP also communicated with representatives of NHLBI about Public Citizen's concerns. Subsequently, the PETAL network, communicating through NHLBI, provided OHRP with its response to Public Citizen's allegations. After reviewing that response, OHRP submitted written questions to the PETAL network through NHLBI, and the PETAL network responded to those questions.

In response to concerns raised by OHRP, along with months of communications between OHRP and NHLBI (and NHLBI working with the PETAL network), as well as comments from site investigators and others, extensive revisions were made to the CLOVERS protocol, from protocol version II (September 2018) to version VI (October 2019). These revisions included corresponding changes to the sample consent form. The following describes what OHRP considers to be the most significant revisions.

Modifications to the CLOVERS Protocol

In general, the key changes to the CLOVERS protocol that have been made since OHRP received Public Citizen's letter are to require closer subject monitoring and to more closely align the treatment of the subjects in the study groups with the care that the subjects might have received had they not participated in the study. More specifically, the protocol has been revised as follows:

1) The protocol explicitly states that an attending physician must confirm, prior to each subject's enrollment, that either study arm would provide good medical care for that potential study subject. Patients will be excluded if the attending physician believes that either study arm is not good clinical care for his or her patient in their clinical judgment. An "Appendix I" was added to provide detailed instructions on how attending physicians should be approached by study team members to determine which subjects are appropriate to enroll in the study.

2) The protocol explicitly states that at any time during the protocol, the clinical team is allowed to provide individualized care, instead of following the study treatment, when such care would be in the best interest of the subject.

3) The Fluids First arm has been modified to align it better to what subjects would receive as usual patient care. Specifically, originally the protocol indicated that two liters of fluid be given to subjects in the Fluids First arm. The revised protocol allows this to be reduced to one liter if,

based on monitoring of the subject's condition, the physician determines that two liters is not necessary. Vasopressors may be administered at any time if the clinical team believes that it is in the best interest of the subject, and then weaned off safely once the fluid boluses have their effect.

4) The protocol was changed to make it clear that the protocolized administration of up to five liters of fluid in the Fluids First arm includes the pre-randomization fluid of up to two liters.

5) The protocol was changed to make it clear that in the Medicine to Raise Blood Pressure First arm, two liters, including pre-randomization fluids, can be provided to subjects, without violating the protocol.

6) The revised protocol provides that rescue fluids may be administered at any time if the clinical team believes that it is in the best interest of the subject.

Modifications to the CLOVERS Consent Form

The consent form has been modified extensively. Key changes to the form include more information about the study procedures and the risks of a subject receiving treatments in the study that differ from what they would have received if they had not participated in the study.

In particular, as originally drafted, the consent form, , in the section titled, "Side effects and risks that are possible if you take part in this study," focused on the side effects of the various treatments that the subjects would receive. It failed to acknowledge that switching a person from one type of treatment for sepsis-induced hypotension to another type of treatment might alter the efficacy of the treatment (e.g., the likelihood that the person might survive), even though that proposition was at the heart of the rationale for conducting the study, as indicated in the hypothesis for the CLOVERS study discussed above. The revised consent form not only includes information about this risk, but it highlights it by positioning it as the very first risk that is described in the risks section of the consent form.

This revision provides information to prospective subjects about one of the main concerns raised by Public Citizen: the risks created by what Public Citizen termed a "misalignment" if a subject is assigned in the CLOVERS study to a treatment that is described as a version of usual care, but that differs from the treatment the subject might have received outside of the trial. Public Citizen was concerned about the difference between treatment closely adhering to the protocol specifications and treatment adjusted by the clinician in response to the individual subject's particular condition.

In addition to the concerns presented in Public Citizen's letter, OHRP raised concerns about the need for the CLOVERS' consent document to include new risk language that also encompasses the risks of providing a subject with either version of the treatments that are being assessed in the CLOVERS study. For example, a subject who might have received a version of "Fluids First" treatment had they not been in the trial, and who was assigned to "Medicine to Raise Blood Pressure First" in the trial, is exposed to various risks from that change in treatment regardless of whether or not both arms accurately represent

how those versions of care would be provided in the clinical setting. The revised language now encompasses those risks.

In particular, the revised "Risks of Study Participation" section now states:

> ***Risks of Study Participation:***
>
> A risk of participating in this study is that assigning you to either the "Medicine to Raise Blood Pressure First" or the "Fluids First" group, by chance (like a coin flip), might lead to treatment that is not as effective as the treatment you might have received outside of the study. Getting treatment that is less effective may hinder your recovery or increase your risk of death. The group treatment you are assigned to receive may cause the risks explained below:
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> Risk of Getting Extra Fluids: Patients in the Fluids First group may get extra fluids through a tube in a vein. It's possible that this could cause stress on your heart related to extra fluid, breathing difficulties, or increased swelling in your arms and legs, which could possibly hinder your recovery and increase the risk of death. This could also cause not enough oxygen to the heart, not enough oxygen to the intestines, not enough oxygen to the kidneys or brain, not enough oxygen to arms, legs, toes or fingers. The chances of these problems may be higher if the fluids are used early.
>
> Risk of Getting Medicine to Raise Blood Pressure: Patients in the Medicine to Raise Blood Pressure First group may receive earlier or more medicine to raise blood pressure. It's possible that this could cause not enough oxygen to the heart, heart rhythm problems, not enough oxygen to the intestines, not enough oxygen to the kidneys or brain, or not enough oxygen to arms, legs, toes, or fingers, which could possibly lead to tissue damage, hinder your recovery, or increase the risk of death. The chances of these problems may be higher if the medicines are used early or before a larger amount of fluids are given.

Conclusion

OHRP believes that the protocol and consent form revisions made by the PETAL Network and accepted by NHLBI appropriately address important concerns raised about the CLOVERS trial. It is our opinion that with these revisions, the study is designed in accordance with the requirements of the HHS regulations for the protection of human subjects at 45 CFR Part 46.

As a general matter, OHRP notes that NHLBI has modified the Funding Opportunity Announcements (FOAs) under which it solicits nearly all clinical trial applications as part of its standard process of regularly updating its clinical trial FOAs in light of the changing clinical trial landscape and informed by discussions with OHRP. These announcements now emphasize that "[i]t is particularly important to provide a discussion of the evidence supporting equipoise" among the trial arms. In their descriptions of their experimental approach, investigators must now describe the "[e]vidence supporting that: 1)

equipoise exists between the arms of the trial and 2) the interventions or control arm(s) tested are not known to be inferior to the range of practice (or usual care) at the sites, in their community, and described in relevant standards of care." These concepts are noted in multiple places in the FOAs and are included in the application review criteria. They can be accessed at: 1) Single-site clinical trials: PAR-19-328 at https://grants.nih.gov/grants/guide/pa-files/PAR-19-328.html, R61/R33; and 2) Multi-site clinical trials: PAR-19-329 at https://grants.nih.gov/grants/guide/pa-files/PAR-19-329.html, UG3/UH3.

NHLBI has also informed OHRP that, as part of its ongoing process of optimizing its clinical trial enterprise, it is examining critical control points in the development and review of clinical trials designs, which includes reinforcing more explicitly the importance of an evidence-based analysis of equipoise and usual care.

We appreciate Public Citizen's continued commitment to the protection of human research subjects. Please contact us if you have any questions or would like additional information.

Sincerely,

Lisa Buchanan

Lisa R. Buchanan, MAOM
Director
Division of Compliance Oversight

cc:
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