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October 13, 2020

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**RE: Project Title: Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis Trial (CLOVERS)**

**Sponsor: National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH)**

**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 Dr. Menikoff and Ms. Buchanan:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, has reviewed your September 28, 2020, letter regarding the alarming ethical and regulatory lapses involving the ongoing NIH-funded CLOVERS that were presented in our August 28, 2018, letter to the Office for Human Research Protections (OHRP).

Although we are somewhat reassured that our 2018 complaint about CLOVERS prompted a deliberative process involving OHRP, NHLBI, and PETAL Network researchers, resulting in “extensive revisions” to the CLOVERS protocol and consent form to address these lapses, we are dismayed by OHRP’s inexcusable failure to take additional necessary actions to protect the rights and welfare of the human subjects who had already been enrolled in the trial prior to our complaint or who were enrolled in the trial subsequent to our complaint but before the extensive revisions to the CLOVERS protocol and consent form were fully implemented. Most disturbing was the persistent failure of the OHRP to require, as we urgently requested in our August 2018<sup>1</sup> and May 2019<sup>2</sup> letters, that enrollment in CLOVERS be suspended until all substantive issues raised in our first letter were assessed, the deliberative process with the NHLBI and PETAL Network researchers was completed, and the extensive revisions to the trial protocol and consent form were finalized and fully implemented.

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<sup>1</sup> Public Citizen. Letter to the Office for Human Research Protections regarding CLOVERS. August 28, 2018. <https://www.citizen.org/wp-content/uploads/2446.pdf>. Accessed October 12, 2020.

<sup>2</sup> Public Citizen. Letter to the Office for Human Research Protections regarding CLOVERS. May 1, 2019. <https://www.citizen.org/wp-content/uploads/2481.pdf>. Accessed October 12, 2020.

The following is a detailed discussion of the disturbing shortcomings in OHRP's response to the ethical and regulatory lapses involving the CLOVERS trial.

### **A. Summary of Public Citizen's August 2018 complaint**

In our original complaint letter, we showed that based on our review of the then-current version of the protocol, sample consent form, and relevant background scientific literature, CLOVERS, as proposed and conducted, 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.<sup>3</sup>

Most notably, CLOVERS as originally designed included only two experimental groups that each involved strategies for management of severe, life-threatening sepsis that deviated substantially from current usual care and were actually unusual care for the early management of sepsis. The trial's lack of a usual-care control group precluded (1) having a benchmark for appropriate monitoring to ensure the safety of enrolled human subjects and (2) the possibility of drawing firm conclusions after the trial is completed that could actually improve and not worsen clinical practice for future patients.

Because the trial's design failed to account for how current usual care for sepsis, with respect to fluid management and use of vasopressors, varies based on the severity of sepsis and patient comorbidities, the two management strategies under investigation would have led 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 and comorbidities, 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 underlying medical condition, resulting in therapies significantly different from what they would have received outside of the clinical trial. The misalignments in CLOVERS as originally designed were so outside the norms of treatment that it was obvious they carried an unacceptable increased risk of organ failure and death and should have been avoided, but the trial's design allowed such risky deviations from usual care in many septic subjects.

As a result of these fundamental flaws in the trial's original design, risks to the subjects enrolled in CLOVERS were not minimized, nor were they reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge expected to result, as required by HHS human subjects protection regulations at 45 C.F.R. §§ 46.111(a)(1) and (2). In addition, the sample consent form approved by the Petal Network Central Institutional Review Board (IRB) failed to adequately describe the nature and reasonably foreseeable risks of the experimental procedures involved in the research, as required by HHS human subjects protection regulations at 45 C.F.R. §§ 46.116(b)(1) and (2).

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<sup>3</sup> Public Citizen. Letter to the Office for Human Research Protections regarding CLOVERS. August 28, 2018. <https://www.citizen.org/wp-content/uploads/2446.pdf>. Accessed October 12, 2020.

**B. OHRP's response to our complaint<sup>4</sup>**

In its September 28, 2020, response, OHRP stated the following:

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. [Emphasis added]

Among the key changes to the CLOVERS protocol described by OHRP were the following:

- (1) 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.
- (2) 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 are 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.
- (3) 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.
- (4) 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.
- (5) 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.

Regarding the CLOVERS consent form changes, the OHRP letter highlighted the following:

**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.** [Emphasis added]

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<sup>4</sup> Office for Human Research Protections. Letter to Public Citizen regarding CLOVERS. September 28, 2020. <https://www.citizen.org/wp-content/uploads/CLOVERS-OHRP-response-to-Public-Citizen-Final-9.28.2020.pdf>. Accessed October 12, 2020.

In particular, as originally drafted, the consent form, , [sic] 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...

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.

OHRP concluded the following:

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.** [Emphasis added]

### **C. Disturbing shortcomings in OHRP’s response**

OHRP’s conclusion that, with the extensive revisions to the CLOVERS protocol and consent form, CLOVERS is now designed in accordance with the requirements of the HHS regulations for the protection of human subjects at 45 C.F.R. Part 46 clearly implies that before protocol version VI (October 2019) was implemented, CLOVERS failed to materially comply with these regulatory requirements. This means that prior to implementation of the extensive protocol revisions described by OHRP, the risks to the subjects enrolled in CLOVERS were not minimized, nor were they reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge expected to result, as required by HHS human subjects protection regulations at 45 C.F.R. §§ 46.111(a)(1) and (2).

Likewise, prior to implementation of the extensive consent form revisions described by OHRP, the sample consent form used to obtain and document informed consent of subjects enrolled in CLOVERS failed to adequately describe the nature and reasonably foreseeable risks of the experimental procedures involved in the research, as required by HHS human subjects protection regulations at 45 C.F.R. §§ 46.116(b)(1) and (2). As a result, the researchers failed to obtain the legally effective informed consent of the subjects.

These circumstances lead us to conclude that OHRP's response to our August 2018 complaint about CLOVERS has had the following unacceptable shortcomings that, among other things, unnecessarily placed hundreds of subjects at increased risk:

***Failure of OHRP to use its authority to suspend enrollment in the trial***

As your response letter acknowledges, on September 11, 2018, Public Citizen — joined by Charles Natanson, M.D., and Peter Eichacker, M.D., two internationally recognized sepsis experts from the NIH Clinical Center who advised Public Citizen — met with OHRP staff to discuss the ethical and regulatory lapses involving CLOVERS that were detailed in our August 2018 letter. It was clear from that meeting that OHRP staff understood the substantive problems with CLOVERS. Indeed, as described in OHRP's letter, our meeting with OHRP staff prompted an intensive deliberative process involving OHRP, NHLBI, and PETAL Network researchers that resulted in extensive revisions to the CLOVERS protocol and consent form to address the ethical and regulatory lapses. OHRP undoubtedly recognized that the CLOVERS protocol and consent form needed significant revisions to protect subjects and remediate alarming ethical and regulatory lapses at least several months, if not a full year, before such revisions were belatedly implemented.

It is our understanding that subject enrollment in CLOVERS was never suspended following OHRP's receipt of our complaint. It is therefore likely that from at least September 2018 until October 2019, hundreds of additional subjects were enrolled in this unethical, high-risk clinical trial that failed to minimize risks to subjects without the subjects being fully informed of the nature and reasonably foreseeable risks of the research.

The failure of OHRP to invoke its authority and suspend subject enrollment in CLOVERS in September 2018 or soon thereafter, while OHRP engaged in further dialogue with the NHLBI and PETAL Network researchers, is inexcusable. OHRP knowingly allowed subjects to be enrolled in a trial that exposed them to unacceptable risk without the subjects being adequately informed of the nature and reasonably foreseeable risks of the research. Such failure represents a stunning abdication of your office's duty to protect the rights, welfare, and wellbeing of human subjects involved in research conducted or supported by HHS. We surmise that OHRP's cowardly inaction occurred for no other reason than a desire for expediency and to avoid ruffling feathers at the NIH.

***Failure of OHRP to require that the PETAL Network researchers develop and implement, with IRB approval, a plan to notify all subjects enrolled in CLOVERS without adequate informed consent***

As OHRP's response letter confirms, the sample consent form that was originally approved by the PETAL Network Central IRB and used to obtain and document the informed consent of subjects enrolled in CLOVERS had serious deficiencies with respect to the description of the nature and reasonably foreseeable risks of the research. As we noted in our August 2018 letter, it is difficult to imagine any reasonable person agreeing to be enrolled in CLOVERS if he or she had been fully informed of the true nature and reasonably foreseeable risks of the trial's experimental interventions as originally designed.

Consistent with the Belmont Report's basic ethical principles of respect for persons, OHRP should have required that the CLOVERS researchers contact the subjects who were enrolled in the trial prior to the implementation of protocol version VI (October 2019) and fully disclose the deficiencies in the design of the trial and in the informed consent information provided at the time of their enrollment. However, because your response letter fails to indicate that OHRP required such follow-up with subjects, we presume that such action has not occurred.

To protect the rights of these subjects, OHRP must mandate that the PETAL Network Central IRB, in conjunction with the CLOVERS researchers, develop a satisfactory plan, including both the means and content, for contacting surviving subjects (or the closest surviving relatives of subjects who are now deceased) who participated in CLOVERS prior to the implementation of protocol version VI (October 2019) and provide them with information about (a) the nature and reasonably foreseeable risks of the research that were not disclosed at the time of their enrollment and (b) the deficiencies in the design of the trial that may have exposed them to unacceptable risk of harm. We note that there is substantial precedent for such OHRP action.

***Failure of OHRP to require that the PETAL Network Central IRB develop a corrective action plan to address serious noncompliance in its review and approval of CLOVERS and to ensure adequate protection of human subject enrolled in future PETAL Network trials***

The alarming ethical and regulatory lapses in the design and conduct of the original CLOVERS protocol that were described in our August 2018 complaint letter and essentially affirmed in OHRP's response letter indicate serious failures by the PETAL Network Central IRB (and any other IRBs that may have reviewed and approved CLOVERS) to ensure that the trial satisfied all criteria for IRB approval under HHS regulations for the protection of human subjects at 45 C.F.R. §§ 46.111.

To ensure the adequate protection of human subjects in future research reviewed by the PETAL Network Central IRB (and any other IRBs that may have reviewed and approved CLOVERS), OHRP should have required that the IRB develop and implement a corrective plan to address these IRB failures. However, because your response letter fails to indicate that OHRP required the development and implementation of a corrective action plan by the IRB, we presume that such action has not occurred. It is imperative that OHRP mandate such action.

Finally, we are concerned that the extensive revisions made to the CLOVERS protocol after the trial was well underway likely will undermine the interpretability of data derived from the trial and confound the overall conclusions that may ultimately be drawn. In effect, the CLOVERS trial now comprises two trials: an initial trial that involved two experimental groups and no usual-care control group and the current trial that involves a quasi-usual-care control group (assuming appropriate actions are taken by clinicians at the bedside to deviate from the protocol when needed) and an altered experimental group. Although it may be statistically possible to combine the data from these two different trials, it is difficult for us to understand how data from these two essentially different trials can be pooled together to support defensible, meaningful interpretations of the results.

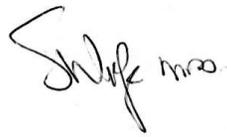
In closing, we urge OHRP to promptly take additional actions to address the major shortcomings in the office's response outlined above. We look forward to hearing from you soon about the additional actions OHRP takes in this matter.

Please contact us if you have any questions or need additional information.

Sincerely,



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Sidney M. Wolfe, M.D.  
Founder and Senior Adviser  
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cc: ADM Brett P. Giroir, M.D., Assistant Secretary for Health, HHS  
Francis S. Collins, M.D., Ph.D., Director, NIH  
Gary H. Gibbons, M.D., Director, NHLBI, NIH