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August 29, 2018

Harvey Murff, M.D., M.P.H.  
Chair, Health Sciences Committee 1 - Institutional Review Board

Sanjay Mohan, M.D.  
Chair, Health Sciences Committee 2 - Institutional Review Board

G. Kyle Rybczyk, R.N.C., F.N.P.  
Chair, Health Sciences Committee 3 - Institutional Review Board  
Human Research Protections Program  
Vanderbilt University Medical Center  
1211 Medical Center Drive  
Nashville, TN 37232

*Delivered by email*

**Re: Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis trial (CLOVERS)**

Dear Dr. Murff, Dr. Mohan, and Mr. Rybczyk:

As you may be aware, Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, yesterday submitted the enclosed letter to the Office for Human Research Protections (OHRP) in which we identified serious ethical and regulatory lapses related to the design and sample consent form of the Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis trial (CLOVERS).

In particular, as a result of the fundamental flaws in the trial's design that are described in detail in our letter to OHRP, risks to the subjects enrolled in CLOVERS are not minimized, nor are they reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge expected to result, as required by Department of Health and Human Services (HHS) human subjects protection regulations at 45 C.F.R. § 46.111(a)(1) and (2). In addition, the sample consent form fails to comply with key provisions of HHS regulations at 45 C.F.R. § 46.116(a).

We are writing to you because (a) Vanderbilt University Medical Center (VUMC) is one of the institutions currently enrolling subjects in CLOVERS, (b) an article published yesterday by *STAT* reported that an institutional review board (IRB) at the VUMC approved CLOVERS,<sup>1</sup> and

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<sup>1</sup> Begley S. Watchdog group calls for NIH to halt 'dangerous' study of sepsis treatment. *STAT*. August 28, 2018. <https://www.statnews.com/2018/08/28/nih-sepsis-study-public-citizen/>. Accessed August 29, 2018.

August 29, 2018

(c) each of you currently chairs one of the three VUMC Health Sciences Committees - IRBs, one of which presumably approved CLOVERS.

If the VUMC IRB that you chair did approve CLOVERS, we respectfully request that you and your IRB take the following actions immediately:

- (1) Review our letter to OHRP so that you understand the serious flaws in the design of the trial that, among other things, result in unacceptable risk of harm to the subjects.
- (2) Immediately suspend the IRB's approval of CLOVERS and direct the CLOVERS investigators to cease enrolling subjects in the trial.

Please note that we would be happy to provide you with copies of all documents cited in our letter to OHRP and its enclosures. We also would be happy to answer any questions that you may have about our critical analysis of the design of CLOVERS.

Public Citizen eagerly awaits VUMC's public notification that it has suspended the IRB's approval of CLOVERS.

Thank you for your attention to this urgent matter regarding the protection of human subjects.

Sincerely,



Michael A. Carome, M.D.  
Director  
Public Citizen's Health Research Group



Sidney M. Wolfe, M.D.  
Founder and Senior Adviser  
Public Citizen's Health Research Group

Enclosure

cc: Jonathan C. Nesbitt, M.D., President, VUMC



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August 28, 2018

Jerry Menikoff, M.D., J.D.  
Director  
Office for Human Research Protections  
U.S. Department of Health and Human Services  
1101 Wootton Parkway, Suite 200  
Rockville, MD 20852

**Re: Project Title: Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis Trial**  
**Sponsor: National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health**  
**Principal Investigator: David A. Schoenfeld, Ph.D., Massachusetts General Hospital, Clinical Coordination 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:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, hereby requests that the Office for Human Research Protections (OHRP) immediately direct NHLBI to terminate enrollment in the Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis trial (CLOVERS) and launch a compliance oversight investigation of the trial and its review and approval by the responsible institutional review board(s) (IRBs). Based on our review of the most recent version of the protocol, sample consent form, and relevant background scientific literature, the trial, as proposed and currently conducted, fails 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.

Our conclusions about the serious regulatory and ethical lapses related to CLOVERS and the resulting unacceptable risks of harm to subjects enrolled in the trial are based on the enclosed critical analysis of the trial's design (see Enclosure A). In preparing this critical analysis, we sought expert advice from Charles Natanson, M.D., Senior Investigator and Chief of the Anesthesia Section in the Critical Care Medicine Department at the National Institutes of Health (NIH) Clinical Center in Bethesda, MD, and Peter Eichacker, M.D., 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 (see Enclosure B for their brief biographic summaries and Web links to their complete curricula vitae).

Most notably, CLOVERS includes only two experimental groups that each involve strategies for management of severe, life-threatening sepsis that deviate substantially from current usual care and are actually unusual care for the early management of sepsis. To our knowledge neither of these two strategies has ever been tested previously in any clinical trial. The trial's lack of a usual-care control group precludes (1) 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.

Furthermore, 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. The misalignments in CLOVERS are so outside the norms of treatment that it is obvious they carry an unacceptable increased risk of organ failure and death and should be avoided, but the trial's design compels such risky deviations from usual care in many septic subjects.

As a result of these fundamental flaws in the trial's design, risks to the subjects enrolled in CLOVERS are not minimized, nor are 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 IRB-approved sample consent form fails to comply with key provisions of HHS regulations at 45 C.F.R. § 46.116(a).

The following is a more detailed discussion of the regulatory and ethical lapses related to CLOVERS.

## **A. Overview of CLOVERS**

On May 21, 2018, Public Citizen requested from the NHLBI under the Freedom of Information Act (FOIA) copies of the most recent versions of the protocol and sample consent forms for CLOVERS. In a June 12, 2018, final response to the FOIA request, the NHLBI provided CLOVERS Protocol Version II (dated November 17, 2017)<sup>1</sup> and an undated sample consent form,<sup>2</sup> which the NHLBI FOIA Office indicated were the most recent versions of these documents. Our understanding of CLOVERS is based on these documents. In a July 16, 2018, final response to another FOIA request for any updated CLOVERS protocol documents, the NHLBI confirmed that CLOVERS Protocol Version II is “the current IRB-approved, active version” of the CLOVERS protocol.

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<sup>1</sup> Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) protocol. Version II. November 17, 2017. [https://www.citizen.org/sites/default/files/clovers\\_protocol\\_versionii\\_111717\\_clean.pdf](https://www.citizen.org/sites/default/files/clovers_protocol_versionii_111717_clean.pdf). Accessed August 22, 2018.

<sup>2</sup> PETAL Network. CLOVERS: Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis draft consent form. Revision date: October 24, 2017. [https://www.citizen.org/sites/default/files/clovers\\_consent\\_with\\_shamroc\\_ancillary.pdf](https://www.citizen.org/sites/default/files/clovers_consent_with_shamroc_ancillary.pdf). Accessed August 22, 2018.

CLOVERS is a multicenter, randomized, unblinded, two-arm clinical trial presently being conducted by a group of academic hospitals called the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network,<sup>3</sup> which succeeded the Acute Respiratory Distress Syndrome (ARDS) Network.<sup>4</sup> The trial, which was recently opened to enrollment, will involve randomly assigning up to 2,320 adult subjects who have sepsis-induced hypotension (low blood pressure) — an often rapidly lethal syndrome with a high mortality rate — to one of two early sepsis management strategies: Subjects in one group receive a management strategy that employs liberal intravenous (IV) fluid administration and restricts use of vasopressors (liberal fluids group), whereas subjects in the other group receive a management strategy that employs restricted IV fluid administration with liberal use of vasopressors (restrictive fluids group) (see Figures A1 and A2 in the Appendix of Enclosure A for a summary of each experimental management strategy).

The inclusion criteria for CLOVERS are:

- (1) Age 18 or older;
- (2) A suspected or confirmed infection (broadly defined by administration or planned administration of antibiotics); and
- (3) Sepsis-induced hypotension defined as systolic blood pressure (SBP) < 100 millimeters of mercury (mmHg) or mean arterial pressure (MAP) < 65 mmHg after a minimum of one liter of fluid (fluids inclusive of pre-hospital fluids; blood pressure must be below any known or reported pre-morbid baseline).

The primary objective of CLOVERS is to determine the impact of the restrictive fluids strategy as compared with the liberal fluids strategy on 90-day in-hospital mortality in patients with sepsis-induced hypotension. The primary outcome measure of the trial is all-cause mortality (death from any cause) prior to discharge home before day 90.

**B. CLOVERS protocol design poses unacceptable risks to subjects and will not contribute important knowledge about improving the management of sepsis.**

As explained in detail in the enclosed critical analysis of the design of CLOVERS, the trial's design is fundamentally flawed in several major respects, including the following:

- (1) The trial includes two experimental groups that each involve strategies for the early management of severe sepsis that to our knowledge have never been tested previously in any clinical trial, but it lacks a usual-care control group.
  - (a) The CLOVERS investigators made no attempt in their protocol to represent the restrictive fluids strategy as being used in any medical facility or as being in any way comparable to usual care at the medical centers included in the PETAL Network. The

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<sup>3</sup> PETAL Network: Prevention & Early Treatment of Acute Lung Injury. <http://petalnet.org/>. Accessed August 22, 2018.

<sup>4</sup> NHLBI ARDS Network. About the NHLBI ARDS Network. <http://www.ardsnet.org/>. Accessed August 22, 2018.

investigators thus appear to recognize that the restrictive fluids strategy is experimental and not consistent with usual care.

- (b) The investigators make claims of the liberal fluids strategy being used clinically but offer no evidence — such as data from (1) an observational study or prospective survey conducted before the trial by themselves or others or (2) a systematic review of the scientific literature of relevant studies in this field — to demonstrate that this management strategy is employed clinically by anyone for usual care of early septic shock.
- (2) The CLOVERS investigators did make several assertions implying that they consider the liberal fluids strategy to be an approximation of usual sepsis care. However, none of the CLOVERS investigators' assertions about this strategy can be substantiated by the information or references provided by the CLOVERS investigators in their protocol. In particular, we noted the following:
- (a) In a recently published report explaining the most current rationale for their trial,<sup>5</sup> the CLOVERS investigators asserted that the liberal fluids strategy will consist of IV fluid management “similar to that of the usual care groups” in the following three recent large, well-documented sepsis trials: Protocolized Care for Early Septic Shock (ProCESS), Australian Resuscitation in Sepsis Evaluation (ARISE), and Protocolised Management in Sepsis (ProMISe).

Our analysis found that the post-randomization early (first six hours) fluid and vasopressor management of subjects who were randomly assigned to the usual-care control groups of the ProCESS, ARISE, and ProMISe trials included fluid volumes that were smaller, administered far less rapidly, and frequently combined with vasopressor therapy compared with the CLOVERS liberal fluids group management strategy. By design, the CLOVERS liberal fluids group protocol administers to subjects with septic shock very aggressive fluid treatment and attempts to markedly limit the use of vasopressors — making this strategy not usual care but unusual care.

- (b) The CLOVERS investigators also asserted that such a liberal fluids strategy dominates current emergency department care in the U.S., is based in part on the initial Surviving Sepsis Campaign (SSC) recommendations and early goal-directed therapy, and is encouraged by the SEP-1 Core Measure from the Centers for Medicare & Medicaid Services and The Joint Commission.<sup>6,7</sup> Our analysis found that in the CLOVERS liberal fluids group, the rapidity with which fluids initially are given, the avoidance of initiating vasopressors until a total of 5 liters of fluids have been administered in subjects with ongoing hypotension or hypoperfusion, and the

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<sup>5</sup> Self WH, Semler MW, Brown SM, et al. Liberal versus restrictive intravenous fluid therapy for early septic shock: Rationale for a randomized trial. *Ann Emerg Med*. 2018 May 9. pii: S0196-0644(18)30315-9. doi: 10.1016/j.annemergmed.2018.03.039. [Epub ahead of print].

<sup>6</sup> *Ibid.*

<sup>7</sup> Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) protocol. Version II. November 17, 2017. [https://www.citizen.org/sites/default/files/clovers\\_protocol\\_versionii\\_111717\\_clean.pdf](https://www.citizen.org/sites/default/files/clovers_protocol_versionii_111717_clean.pdf). Accessed August 22, 2018.

level of hypotension allowed before administering vasopressors are inconsistent with both the recommendations of these critical care society SSC guidelines and the U.S. government's SEP-1 performance measures. Fluid and vasopressor management in the CLOVERS liberal fluids group protocol deviate substantially from the recommendations of the SSC guidelines and bundle and the SEP-1 performance measures.

Thus, the CLOVERS investigators have designed a trial that compares two management strategies of early care for septic shock, each of which differs fundamentally from the other strategy but both of which differ substantially from usual care as described by sources cited by the investigators. Indeed, in designing CLOVERS, the investigators intentionally sought to ensure that there would be marked differences between the two experimental groups with respect to the amounts of fluids and vasopressors given to subjects. This maximizes the chance that a difference in mortality between the two groups will be found while also increasing the risks for the subjects in both groups.

One particularly troubling aspect of the liberal fluids management strategy is that septic shock subjects could remain severely hypotensive (i.e., SBPs between 70 and 90 mmHg and MAPs between 47 and 60 mmHg) for several hours without vasopressors being administered. Such blood pressure levels would be far below the level that septic shock patients are commonly allowed to fall to or remain at for hours before vasopressors would be started. Many clinicians would view such low and life-threatening blood pressure as an emergency requiring both fluids and vasopressors to be administered as rapidly as possible to raise pressures to safer levels.

- (3) Because septic shock is a potentially rapidly lethal clinical syndrome with a high mortality rate, if a new intervention being tested in a clinical trial is harmful, it will likely add to the organ failure and mortality that are part of the natural history of sepsis. However, without an adequate usual-care control group for comparison to the mortality rate that would occur outside of the trial in similar patients managed according to current usual care, it will be impossible to determine, as the trial progresses, whether one or both of the management strategies being studied is harmful compared with usual care. Additionally, if both strategies are harmful but neither is substantially different from the other, enrollment will continue and put more subjects at unnecessary risk, because the mortality rate in a usual-care control group will not be available to determine whether the trial should be stopped for harm.

In addition, in the absence of a usual-care control group, it is difficult to understand what conclusions can ultimately be drawn from CLOVERS that will guide potential modifications to improve usual-care practices for the early resuscitation of septic shock because the investigators are not studying usual care. It is evident that in either trial group, restricting the early use of one of the two major cardiovascular treatments for resuscitation of septic shock could worsen outcomes. Thus, one of the two experimental sepsis strategies may have a better survival rate than the other in CLOVERS, but it will not be possible to determine whether it is better (or worse) than current usual care. This trial design will only allow the conclusion that if the two treatment strategies studied are the only two therapeutic options allowed for septic shock (which is never the case), the

strategy associated with the worse outcome should not be used. However, it cannot be concluded that the other strategy is the one that should be used. This is because neither of the two “unusual-care” experimental strategies would have been compared with current usual care and shown to be equivalent to or better than usual care. Moreover, the conclusion of the trial could be to recommend a sepsis management strategy that, although better than the other strategy, is actually more harmful than current usual care and, if adopted, will harm countless septic shock patients in perpetuity.

- (4) 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 the usual care they would have received outside of the clinical trial. In the case of CLOVERS, the trial design fails to account for the wide range of disease severity among sepsis patients and the titration and balancing of IV fluids and vasopressors based on sepsis severity to maximize their benefits and limit their risks during usual care for early sepsis. For this reason, the CLOVERS design will result in dangerous misalignments of the two extreme interventions being tested in CLOVERS with the different levels of septic shock severity for subjects randomly assigned to each experimental group. The misalignments in CLOVERS are so outside the norms of treatment that it is obvious they carry an unacceptable increased risk of organ failure and death and should be avoided, but the trial’s design will compel such risky deviations from usual care in many septic subjects.

Importantly, even the inclusion of a usual-care control group would not address these perilous misalignments for subjects in the two experimental groups.

As a result of these numerous serious fundamental flaws in the design of CLOVERS, it is impossible for the trial to satisfy the following criteria required for IRB approval of human subjects research under HHS regulations for the protection of human subjects at 45 C.F.R. § 46.111(a), which are grounded in the Belmont Report’s basic ethical principle of beneficence:<sup>8</sup>

- (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 C.F.R. § 46.111(a)(1)).
- (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 C.F.R. § 46.111(a)(2)).

By not defining usual care for early sepsis in any manner to guide the design of CLOVERS, it appears that the investigators essentially concocted the two experimental sepsis management strategies being tested in the trial out of thin air. It is clear that the two strategies (i) deviate substantially from usual care for sepsis, (ii) lack scientific evidence to support their use, and (iii) create dangerous “misalignments” in care for subjects with different levels of septic shock

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<sup>8</sup> National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Ethical principles and guidelines for the protection of human subjects of research. April 18, 1979. <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html>. Accessed August 22, 2018.

severity who are randomly assigned to each experimental group. As a result, the CLOVERS investigators have designed a trial that not only fails to minimize risks to subjects, but actually increases risks of serious harm, including risk of organ failure and death.

Finally, we note that the CLOVERS protocol includes the following two exclusion criteria, among others:

- (1) Treating physician unwilling to give additional fluids as directed by the liberal protocol
- (2) Treating physician unwilling to use vasopressors as directed by the restrictive protocol

These exclusion criteria cannot overcome the serious fundamental flaws in the design of CLOVERS. In particular, we note that because both the liberal fluids and restrictive fluids management strategies deviate substantially from usual care for early sepsis management and to our knowledge have never been tested previously in any clinical trial, there is no scientific or clinical experience base that would allow treating physicians to adequately judge whether any potential subject with severe sepsis could be safely randomized to either experimental group.

### **C. Inadequate informed consent**

Consistent with the Belmont Report's basic ethical principles of respect for persons, HHS regulations for the protection of human subjects at 45 C.F.R. § 46.116(a) require that when seeking the consent of prospective subjects for research, investigators provide, among other things, the following information:

- (1) A description of the procedures to be followed and identification of any procedures that are experimental (45 C.F.R. § 116(a)(1))
- (2) A description of any reasonably foreseeable risks or discomforts to the subject (45 C.F.R. § 46.116(a)(2))

Based on our analysis of the CLOVERS protocol, we find that the most recent version of the sample consent form<sup>9</sup> that was provided to us by NHLBI and that apparently was reviewed and approved by the PETAL Network Central IRB is seriously deficient with respect to these basic elements of informed consent. However, simply revising the consent form to address these deficiencies would not be sufficient to address the serious regulatory and ethical lapses related to CLOVERS protocol's fundamentally flawed design and to salvage the trial.

Regarding the procedures to be followed and identification of any procedures that are experimental, the CLOVERS sample consent includes the following pertinent statements scattered across various sections:

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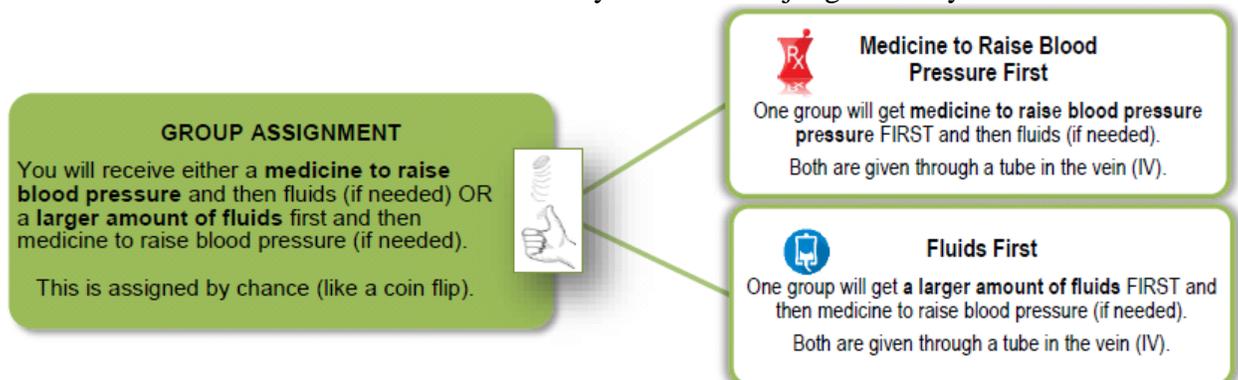
<sup>9</sup> PETAL Network. CLOVERS: Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis draft consent form. Revision date: October 24, 2017. [https://www.citizen.org/sites/default/files/clovers\\_consent\\_with\\_shamroc\\_ancillary.pdf](https://www.citizen.org/sites/default/files/clovers_consent_with_shamroc_ancillary.pdf). Accessed August 22, 2018.

### *What is the purpose of this study?*

You are invited to take part in a research study of different ways to use “intravenous fluids” (fluids given through a small tube placed in your vein) and “vasopressors” (medicines used to raise blood pressure) to treat “sepsis,” (a serious infection). ... We do not know which approach is better in this situation: a) starting medicines to raise blood pressure first and then giving more fluids (if needed), or b) giving a larger amount of fluids first and then giving medicines to raise blood pressure if needed. Right now, the choice of approach is left to the doctors. **Some doctors use medicines to raise blood pressure followed by extra fluids, and others use extra fluids followed by medicines to raise blood pressure. Some doctors use a combination of the two** [emphasis added]. This treatment part of the study will last for 24 hours, and then we will follow you until you go back to where you live. We want to find out whether one of these approaches compared to the other can improve a patient’s chances of survival. ...

### *What will happen and how long will you be in the study? ...*

Before entering the study, you received an amount of fluids through a tube placed in your vein. After getting these fluids you will be put into one of the two study groups (see below). You will be in that group for 24 hours. After 24-hours, your doctor will decide how the medicine to raise blood pressure and fluids will be given (if they are still needed). All other treatments, medicines (such as antibiotics), and procedures commonly used for this condition are allowed in this study based on the judgment of your doctors.



### **During the study:**

- ☑ **We will talk with your doctors.** The research team will inform your doctors about you being in this study. You will receive all other medications (e.g. antibiotics) and treatments that your doctors decide you need. The study team and your doctors and nurses will work together to give you intravenous fluids and medicines to raise your blood pressure based on the treatment protocol that you are assigned to and based on your needs. ...

***Side effects and risks that are possible if you take part in this study***

- Risk of Getting Extra Fluids: Patients in the [liberal fluids] group may get extra fluids through a tube in a vein. ...
- Risk of Getting Medicine to Raise Blood Pressure: Patients in the [restrictive fluids] group may receive earlier or more medicine to raise blood pressure. ...

***Risks that are not known ...***

Although both fluids through a tube in a vein and vasopressors are commonly used in the care of this condition ...

None of the above statements informs prospective subjects (or their legally authorized representatives) that both the liberal fluids and restrictive fluids management strategies are experimental and deviate substantially from the usual care for early sepsis that most of the subjects would otherwise receive if they were not enrolled in CLOVERS. Nor does the consent form explain to subjects the specific significant deviations from usual care that will occur for each trial group. For example, there is no mention of the fact that subjects randomly assigned to the liberal fluids group could remain severely hypotensive (i.e., SBPs between 70 and 90 mmHg and MAPs between 40 and 60 mmHg) for several hours without vasopressors being administered when such blood pressure levels would be far below the level that septic shock patients are commonly allowed to fall to or remain at for hours before vasopressors would be started.

More troublingly, cursory statements like “[s]ome doctors use medicines to raise blood pressure followed by extra fluids, and others use extra fluids followed by medicines to raise blood pressure;” “[s]ome doctors use a combination of the two;” and “both fluids through a tube in a vein and vasopressors are commonly used in the care of this condition” misleadingly imply that both experimental management strategies are used commonly in usual care of sepsis, though they clearly are not.

Regarding reasonably foreseeable risks, the CLOVERS sample consent form includes the following key statements that purportedly explain the risks of the research:

***Side effects and risks that are possible if you take part in this study***

- Risk of Getting Extra Fluids: Patients in the [liberal fluids] 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.
- Risk of Getting Medicine to Raise Blood Pressure: Patients in the [restrictive fluids] 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, or not enough oxygen to arms, legs, toes, or fingers. The chances of these problems may be higher if the medicines are used early or before a larger amount of fluids are given. ...

- Risk of Death We do not know whether your risk of dying from your serious infection will be changed by choosing to be in this study. ...

### ***Risks that are not known***

We do not know whether your risk of dying will be higher or lower if you choose to be in this study.

The above statements represent a markedly oversimplified and incomplete presentation of the reasonably foreseeable risks of CLOVERS. Strikingly absent from this description are the reasonably foreseeable risks of (i) *not* receiving vasopressors that many subjects would otherwise receive as part of usual care for sepsis outside the context of the trial and (ii) *not* receiving additional IV fluids that many subjects would otherwise receive as part of usual care for sepsis outside the context of the trial. For example, there is no mention of the risks to subjects randomly assigned to the liberal fluids group that could result from remaining severely hypotensive (i.e., SBPs between 70 and 90 mmHg and MAPs between 47 and 60 mmHg) for several hours without vasopressors being administered when such blood pressure levels would be far below the level that septic shock patients are commonly allowed to fall to or remain at for hours before vasopressors would be started. Moreover, the consent form fails to disclose the reasonably foreseeable risks that will result from the significant and dangerous misalignments of the two extreme interventions being tested in CLOVERS with the level of septic shock severity for subjects randomly assigned to each experimental group noted in our critical review. Contrary to the above misleading statements noting uncertainty about the risk of death, it is reasonably foreseeable that some subjects enrolled in CLOVERS are more likely to die or have serious organ failure because of the prolonged periods of hypotension or hypovolemia that are permitted under the trial protocol, as well as the dangerous misalignments in care that will occur in many subjects.

It is difficult to imagine any reasonable person agreeing to enroll in CLOVERS if he or she were fully informed of the true nature and risks of the trial's experimental interventions.

### **D. Conclusions and requested actions**

In summary, the regulatory and ethical lapses in the rationale and design of the CLOVERS protocol and in the content of the trial's sample consent form are stunning in their breadth and scope.

The design of the CLOVERS trial is more akin to an experiment that would be conducted on laboratory animals in which two sets of experimental procedures that have no basis in usual clinical care of sepsis are being studied in order to examine the underlying pathophysiology of severe sepsis. The human subjects of the CLOVERS trial, as designed and currently conducted, are unwitting guinea pigs in a physiology experiment that will not advance medical care for sepsis. The fact that this trial successfully passed through multiple levels of review and was approved by officials at the NHLBI and the PETAL Network Central IRB (and perhaps the IRBs of other PETAL Network institutions; see Enclosure C for a list of institutions identified on the

ClinicalTrials.gov website as study locations for CLOVERS<sup>10</sup>) is yet another troubling example of the dysfunction — at multiple levels — of the U.S. system for protecting human subjects enrolled in complex clinical trials.

We therefore urge the OHRP to immediately direct NHLBI to terminate enrollment in CLOVERS and launch a compliance oversight investigation of the trial and its review and approval by the the PETAL Network Central IRB (and any other IRB that approved the trial). Among the key questions that must be addressed in OHRP's investigation of CLOVERS are the following:

- (1) Among the membership of the PETAL Network Central IRB (and any other IRB that approved CLOVERS), were there any members with expertise in management of septic shock and, if so, did those members participate in the review and approval of CLOVERS?
- (2) During its review of CLOVERS, did the PETAL Network Central IRB (and any other IRB that approved CLOVERS) ask the CLOVERS investigators to provide (a) a detailed description of the use of intravenous fluids and vasopressors in usual-care management of sepsis patients; (b) evidence to demonstrate that the CLOVERS liberal fluids management strategy is used clinically by anyone for usual care of early septic shock; and (c) clarification regarding the differences between usual-care management for sepsis and each of the two management strategies being tested in CLOVERS? If so, how did the CLOVERS investigators respond to any such requests?

Finally, we urge OHRP to require NHLBI to place a moratorium on all other current PETAL Network clinical trials and any other NHLBI-funded clinical trials testing interventions in critically ill subjects until the systemic breakdowns that permitted the fundamentally flawed CLOVERS to be approved in the first place are fully understood and corrected.

Please note that the OHRP may share our complaint letter, with identifiers, with anyone. We will be posting a copy on Public Citizen's website as well.

Thank you for your prompt attention to this important matter regarding the protection of human subjects. We look forward to the OHRP's thorough and careful investigations into the serious regulatory and ethical lapses related to CLOVERS.

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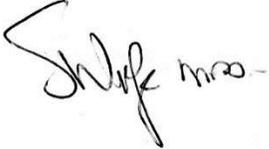
<sup>10</sup> U.S. National Library of Medicine. ClinicalTrials.gov. Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS). Updated May 28, 2018. <https://clinicaltrials.gov/ct2/show/study/NCT03434028>. Accessed August 22, 2018.

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

Sincerely,



Michael A. Carome, M.D.  
Director  
Public Citizen's Health Research Group



Sidney M. Wolfe, M.D.  
Founder and Senior Adviser  
Public Citizen's Health Research Group

Enclosure A: Critical Analysis of the Design of CLOVERS

Enclosure B: Brief biographic summaries and Web links to complete curricula vitae of experts who advised Public Citizen

Enclosure C: List of PETAL Network Institutions Identified on the ClinicalTrials.gov Website as Study Locations for CLOVERS

cc: The Honorable Alex M. Azar, Secretary of Health and Human Services  
ADM Brett P. Giroir, M.D., Assistant Secretary for Health, HHS  
Gary H. Gibbons, M.D., Director, NHLBI, NIH

**Enclosure A: Critical Analysis of the Design  
of CLOVERS**

# A Critical Analysis of the Design of CLOVERS

## August 28, 2018

### *Introduction*

The Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis Trial (CLOVERS)<sup>1,2</sup> is a multicenter, randomized, unblinded, two-arm clinical trial presently being conducted by a group of academic hospitals called the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network,<sup>3</sup> previously known as the Acute Respiratory Distress Syndrome (ARDS) Network.<sup>4</sup> Funding for CLOVERS is provided by the National Heart, Lung, and Blood Institute. The primary objective of the trial is to compare the effect on mortality of an early *liberal fluids-restrictive vasopressors* management strategy (liberal fluids group) (See Figure A1, Appendix) with an early *restrictive fluids-liberal vasopressors* strategy (restrictive fluids group) (see Figure A2, Appendix) in patients with sepsis-induced hypotension.

The investigators claim that there is real debate among clinicians over which of these two strategies should be used to manage early sepsis.<sup>5</sup> However, the CLOVERS investigators provided no data that support this assertion. Specifically, the investigators failed to show directly that either management strategy is used, let alone preferred, by caregivers in the usual-care management of early sepsis. First, the CLOVERS investigators made no attempt in their protocol to represent the restrictive fluids strategy as being used in any medical facility or as being in any way comparable to usual care at the participating PETAL Network medical centers. The investigators thus appear to recognize that the restrictive fluids strategy is experimental and not consistent with usual care. Second, the investigators make claims of the liberal fluids strategy being used clinically but offer no evidence — such as data from (1) an observational study or prospective survey conducted before the trial by themselves or others or (2) a systematic review of the scientific literature of relevant studies in this field — to demonstrate that this management strategy is employed clinically by anyone for usual care of early septic shock. As we will show, the liberal fluids management strategy in CLOVERS is also not usual care.

To our knowledge, neither management strategy has ever been used clinically or evaluated previously in any clinical trial, and both represent untested experimental strategies for the early management of sepsis.

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<sup>1</sup> Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) protocol. Version II. November 17, 2017. [https://www.citizen.org/sites/default/files/clovers\\_protocol\\_versionii\\_111717\\_clean.pdf](https://www.citizen.org/sites/default/files/clovers_protocol_versionii_111717_clean.pdf). Accessed August 22, 2018.

<sup>2</sup> Self WH, Semler MW, Brown SM, et al. Liberal versus restrictive intravenous fluid therapy for early septic shock: Rationale for a randomized trial. *Ann Emerg Med*. 2018 May 9. pii: S0196-0644(18)30315-9. doi: 10.1016/j.annemergmed.2018.03.039. [Epub ahead of print]

<sup>3</sup> PETAL Network: Prevention & Early Treatment of Acute Lung Injury. <http://petalnet.org/>. Accessed August 22, 2018.

<sup>4</sup> NHLBI ARDS Network. About the NHLBI ARDS Network. <http://www.ardsnet.org/>. Accessed July 12, 2018.

<sup>5</sup> Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) protocol. Version II. November 17, 2017. [https://www.citizen.org/sites/default/files/clovers\\_protocol\\_versionii\\_111717\\_clean.pdf](https://www.citizen.org/sites/default/files/clovers_protocol_versionii_111717_clean.pdf). Accessed July 12, 2018.

In a recently published report explaining the most current rationale for their trial, the CLOVERS investigators did make the following assertions in an attempt to justify the trial's liberal fluids management strategy:<sup>6</sup>

A "liberal" fluids approach to septic shock management is characterized by the administration of several liters (typically 50 to 75 mL/kg) of intravenous fluid during the first several hours of treatment. Vasopressor infusions are added immediately if the patient is profoundly hypotensive (eg, systolic blood pressure <70 mm Hg) or remains hypotensive despite large-volume fluid resuscitation. **This liberal fluids strategy dominates current ED [emergency department] care in the United States**, based in part on the initial Surviving Sepsis Campaign recommendations and early goal-directed therapy. A liberal fluids approach is also encouraged by the SEP-1 Core Measure from the Centers for Medicare & Medicaid Services and The Joint Commission, which recommends an infusion of at least 30 mL/kg of crystalloid fluid within 3 hours of septic shock recognition. ...

The liberal [fluids] strategy will consist of intravenous fluid management **similar to that of the usual care groups** in [the three sepsis trials] ProCESS [Protocolized Care for Early Septic Shock], ARISE [Australian Resuscitation in Sepsis Evaluation], and ProMISE [Protocolised Management in Sepsis], in which fluid administration is encouraged as first-line treatment for signs of hypoperfusion without overt fluid overload.

[Emphasis added]

These assertions imply that the investigators consider the liberal fluids strategy to be an approximation of usual sepsis care. Therefore, we carefully examined the sources cited by the CLOVERS investigators in their protocol to determine whether the liberal fluids management strategy does indeed approximate usual care as described in these sources. We found that none of the CLOVERS investigators' assertions about this strategy can be substantiated by the information or references provided by the CLOVERS investigators themselves.

It is clear from our analysis that CLOVERS does not include an actual usual-care control group based on the sources cited by the investigators. We will show that the trial's lack of a usual-care control group precludes (1) appropriate monitoring to ensure the safety of enrolled human subjects and (2) drawing firm conclusions after the trial is completed that will actually improve and not worsen clinical practice for future patients.

Furthermore, we will show that because the trial's design does not account for how current usual care varies based on the severity of sepsis with which individual subjects enrolling in the trial will present, the two management strategies under investigation will actually lead to

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<sup>6</sup> Self WH, Semler MW, Brown SM, et al. Liberal versus restrictive intravenous fluid therapy for early septic shock: Rationale for a randomized trial. *Ann Emerg Med*. 2018 May 9. pii: S0196-0644(18)30315-9. doi: 10.1016/j.annemergmed.2018.03.039. [Epub ahead of print]. The section of the CLOVERS protocol (Version II, November 17, 2017) that discussed the rationale for the liberal fluids strategy had very similar statements, but we chose to quote from the Self et al paper here because it is the most recent publicly available document (received for publication on February 6, 2018; revision received March 25, 2018).

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. The misalignments in CLOVERS are so outside the norms of treatment that it is obvious they carry an unacceptable increased risk of organ failure and death and should be avoided, but the trial's design will compel such risky deviations from usual care in many septic subjects.

### ***Methods Used to Compare the CLOVERS Liberal Fluids Group Protocol with Usual Care***

We first determined whether there are substantive differences between the liberal fluids group protocol in CLOVERS and the management of usual-care control group subjects in the prior three sepsis trials that were referenced by the investigators and that failed to confirm the benefits of early goal-directed therapy (ProCESS,<sup>7</sup> which was conducted in the United States; ARISE,<sup>8</sup> which was conducted mostly in Australia and New Zealand; and ProMISe,<sup>9</sup> which was conducted in England). We calculated from the published reports how fluids and vasopressors were given immediately before and early on (up to six hours) after randomization in the control groups of these sepsis trials and compared this with how these two interventions would be given if the CLOVERS liberal fluids group protocol was followed over this same period.

We next compared the liberal fluids group protocol with recommendations for the early treatment of septic shock with fluids and vasopressors drawn from the same national critical care society guidelines and government-sponsored performance measures that were referenced by the investigators in support of their statement asserting that a liberal fluids strategy dominates current emergency department care for sepsis in the U.S.

Finally, we assessed whether claims in the CLOVERS protocol about how fluids and vasopressors are commonly used for septic shock management are substantiated in the other cited references.

### ***The CLOVERS Liberal Fluids Group Protocol<sup>10</sup>***

Patients are eligible to be enrolled in the CLOVERS trial if, within 4 hours of presentation, they demonstrate evidence of septic shock manifested by persistent hypotension (systolic blood pressure [SBP] <100 millimeters of mercury [mmHg] or mean arterial blood pressure [MAP] <65 mmHg) after receiving 1 to 3 liters (L) of intravenous (IV) fluids. Subjects randomized to

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<sup>7</sup> Yealy DM, Kellum JA, Huang DT, et al; ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. *N Engl J Med.* 2014;370(18):1683-1693.

<sup>8</sup> ARISE Investigators; ANZICS Clinical Trials Group, Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med.* 2014;371(16):1496-1506.

<sup>9</sup> Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med.* 2015;372(14):1301-1311.

<sup>10</sup> Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) protocol. Version II. November 17, 2017. [https://www.citizen.org/sites/default/files/clovers\\_protocol\\_versionii\\_111717\\_clean.pdf](https://www.citizen.org/sites/default/files/clovers_protocol_versionii_111717_clean.pdf). Accessed August 22, 2018.

the liberal fluids group will immediately begin receiving a 2-L IV fluid bolus to be completed within two hours. Notably, subjects receiving vasopressors at the time of randomization in the liberal fluids group are to have them titrated off as soon as possible after randomization.

After the 2-L IV fluid bolus, subjects are to receive additional 0.5-L IV fluid boluses if there is evidence of ongoing hemodynamic instability and tissue hypoperfusion (see Figure A.1, Appendix, for details).

After the post-randomization 2-L IV fluid bolus is completed but *before* total IV fluid administration (pre- and post-randomization) reaches 5 L, vasopressors are only permitted (but are not required) in the liberal fluids group if any of the following criteria are met: (1) SBP <70 mmHg for at least five minutes; (2) clinical manifestations of fluid overload; (3) lactate >4 millimoles (mmol)/L and rising from a previous lactate after at least 2 hours of therapy; or (4) suspected central or peripheral ischemia or presence of mottling.

After total IV fluid administration (pre- and post-randomization) reaches 5 L, vasopressors are allowed if any of the four aforementioned criteria are met or if the SBP is <90 mmHg, and the protocol instructs clinicians to “consider” (but they are not required to initiate) a norepinephrine infusion titrated to maintain MAP >65 mmHg.

### ***Usual-Care Fluid and Vasopressor Treatment Pre-randomization in the ProCESS, ARISE, and ProMISe Trials Versus the CLOVERS Enrollment Criteria***

Septic shock patients were enrolled in the ProCESS,<sup>11</sup> ARISE,<sup>12</sup> and ProMISe<sup>13</sup> trials if they remained hypotensive (MAP <65 mmHg or SBP <90 mmHg) after receiving at least 1 L of fluid resuscitation, if they had evidence of hypoperfusion based on a serum lactate level  $\geq 4$  mmol/L, or both. In all three trials, subjects had to be enrolled within two hours after fulfillment of all inclusion criteria. Subjects randomly assigned to usual care in the ProCESS (n = 456), ARISE (n = 798), and ProMISe (n = 626) trials received IV fluid amounts pre-randomization (mean $\pm$ standard deviation [SD]) of 2.1 $\pm$ 1.4 L, 2.6 $\pm$ 1.3 L, and 2.0 $\pm$ 1.1 L, respectively. These volumes are comparable to the 1 to 3 L of fluid subjects are allowed to receive pre-enrollment in CLOVERS.<sup>14</sup> Thus, the pre-randomization fluid volumes for the CLOVERS protocol are similar to the amounts of fluids given before randomization to subjects in the usual-care control groups in the three earlier trials.

Septic shock subjects in CLOVERS can receive vasopressors pre-randomization if necessary and still be eligible to be enrolled. The percentage of subjects receiving vasopressors pre-

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<sup>11</sup> Yealy DM, Kellum JA, Huang DT, et al; ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. *N Engl J Med.* 2014;370(18):1683-1693.

<sup>12</sup> ARISE Investigators; ANZICS Clinical Trials Group, Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med.* 2014;371(16):1496-1506.

<sup>13</sup> Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med.* 2015;372(14):1301-1311.

<sup>14</sup> Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) protocol. Version II. November 17, 2017. [https://www.citizen.org/sites/default/files/clovers\\_protocol\\_versionii\\_111717\\_clean.pdf](https://www.citizen.org/sites/default/files/clovers_protocol_versionii_111717_clean.pdf). Accessed August 22, 2018.

randomization in the usual-care control groups of ProCESS, ARISE, and ProMISe were 15.1%, 21.7%, and 3.4%, respectively.

***Fluid and Vasopressor Management After Randomization Comparing the Usual-Care Control Groups of the Three Trials with the CLOVERS Liberal Fluids Group Protocol***

Data provided from the ProCESS, ARISE, and ProMISe trials showed that, over the six hours after randomization, the cumulative volumes of fluids (mean±SD) that usual-care control group subjects with septic shock received were 2.3±1.9 L, 1.7±1.4 L and 2.0±1.3 L, respectively. These mean amounts are close to the total amount of fluids all CLOVERS subjects in the liberal fluids group should receive in no more than two hours if the protocol is followed. These mean amounts also were administered in the three trials much more slowly, over six hours, than the 2 L that must be administered over two hours in the CLOVERS protocol. Moreover, assuming that this zero to six hours fluid data from the three trials is normally distributed, a substantial percentage of the usual-care septic shock subjects actually received far less than 2 L of fluid over this entire six-hour period (approximately 44% for ProCESS, 58% for ARISE, and 49% for ProMISe).

Data provided from the ProCESS and ProMISe trials also delineated the fluid volumes delivered each hour in usual-care control group subjects with septic shock over the six hours after enrollment. Assuming that this data (extrapolated from the figures) was independent and normally distributed, the cumulative fluid volume delivered to the usual-care control group subjects in the ProCESS and ProMISe trials from zero to two hours (mean±SD) were only approximately 1.2±0.9 L and 1.4±0.9 L, respectively. This is much less than the 2-L fluid volume all subjects will be assigned to receive in the CLOVERS liberal fluids group over this initial two hours. In fact, 70% or more of the usual-care control group subjects with septic shock in the two trials would have gotten less than 2 L of fluids during the initial two hours. Even from zero to three hours, the cumulative amounts of fluids that usual-care control group subjects received in the ProCESS and ProMISe trials were approximately 1.5±1.0 L and 1.8±0.9 L, respectively, and 60% or more of these control subjects had still received less than 2 L of fluids. Therefore, based on data from the three trials, the protocol for the CLOVERS liberal fluids group represents by design a substantial increase in the rapidity and total amount of fluids that patients would receive early on after randomization compared with usual care for septic shock.

In CLOVERS, after receiving 1 to 3 L of pre-randomization fluids, the management goal for septic shock subjects enrolled in the liberal fluids group is to receive fluids *without vasopressors*. After randomization, a 2-L fluid bolus is to be administered over no more than two hours, during which time use of vasopressors is not an option according to the management algorithm for the liberal fluids group (see Figure A.1). After the post-randomization 2-L IV fluid bolus is completed but *before* total IV fluid administration (pre- and post-randomization) reaches 5 L, vasopressors are permitted (but are not required) in the liberal fluids group if SBP is less than 70 mmHg for at least five minutes. Therefore, septic shock subjects in the liberal fluids group could remain severely hypotensive for several hours with SBPs between 70 and 90 mmHg. Notably, septic shock commonly produces very low diastolic blood pressures, which with SBPs between 70 and 90 mmHg could be 35 to 45 mmHg. These systolic and diastolic blood pressures in combination would result in dangerously low MAPs of between 47 and 60 mmHg. Such blood

pressure levels would be far below the level that septic shock patients are commonly allowed to fall to or remain at for hours before vasopressors would be started.

To understand the proportion of septic shock patients who would typically be administered vasopressors early on, we examined data from the ProCESS, ARISE, and ProMISe trials that showed the percentage of usual-care control group subjects with septic shock who received vasopressors during the six hours following randomization. The data revealed that 44%, 58%, and 47%, respectively, of control group subjects in these trials received vasopressors during this time. The ProMISe trial investigators further reported the percentage of usual-care control group subjects with septic shock who received vasopressors each hour for the first six hours following randomization. In these subjects receiving usual care for severe sepsis, the proportion that received vasopressors (data extrapolated from the figures) progressively increased from approximately 23% at zero-to-one hours to approximately 32% at one-to-two hours and 44% at five-to-six hours. During this same time, the SBP (mean±SD) increased from approximately 98±26 at zero hours to approximately 103±23 at one hour, 108±25 at two hours, and 111±22 at six hours. Thus, contrasting these data with the CLOVERS protocol shows that a substantial number of subjects randomly assigned to the liberal fluids group in CLOVERS would not receive vasopressor treatment that they would have received from zero to six hours with usual care to avoid very low blood pressures. Furthermore, based on the above data, SBPs between 70 and 90 mmHg without vasopressor support were uncommonly reached for subjects in the usual-care control group of the ProMISe trial.

Overall, compared with the CLOVERS liberal fluids group protocol, usual care in the large, well-documented ProCESS, ARISE, and ProMISe trials included fluid volumes that were smaller, administered far less rapidly, and frequently combined with vasopressor therapy. By design, the CLOVERS liberal fluids group protocol administers septic shock subjects very aggressive fluid treatment and attempts to markedly limit use of vasopressors — making this strategy not usual care but unusual care. As a result, contrary to the assertions of the CLOVERS investigators, the management strategy for the liberal fluids group is not “similar to that of the usual care [control] groups in ProCESS, ARISE, and ProMISe.” Instead, the CLOVERS liberal fluids group represents a second experimental group, not a control group. Indeed, in designing CLOVERS, the investigators intentionally sought to ensure that there would be marked differences between the liberal fluids group and the restrictive fluids group with respect to the amounts of fluids and vasopressors given to subjects. This maximizes the chances that a difference in mortality between the two groups will be found while also increasing the risks for the subjects in both groups, but neither group’s management strategy will simulate usual care for septic shock.

***Comparison of Early Management in the CLOVERS Liberal Fluids Group Versus Early Treatment of Septic Shock Required in Government-Sponsored Performance Measures and Recommended by National Critical Care Societies***

As previously noted, in their discussion of the rationale for the liberal fluids strategy, the CLOVERS investigators asserted that such a strategy dominates current emergency department care in the U.S., is based in part on the initial Surviving Sepsis Campaign (SSC) recommendations and early goal-directed therapy, and is encouraged by the Severe Sepsis and

Septic Shock Early Management Bundle (SEP-1) Core Measure from the Centers for Medicare and Medicaid Services (CMS) and The Joint Commission.<sup>15,16</sup> We therefore compared the CLOVERS liberal fluids protocol with these sepsis management recommendations and the SEP-1 performance measures.

The CMS SEP-1 performance measures for 2018 requires that patients presenting with severe sepsis and hypotension receive 30 mL/kg of fluids (e.g., approximately 2.1 L for a 70-kg patient) within three hours (not 3 to 5 L within six hours, as in the CLOVERS liberal fluids group protocol) and that, if hypotension persists after this fluid administration, they receive vasopressors.<sup>17,18</sup> Therefore, SEP-1 requires all septic shock patients who weigh approximately 70 kg and are persistently hypotensive after receiving approximately 2 L of total fluid to begin receiving vasopressors immediately, not to wait six or more hours until 5 liters are given, as would occur in the CLOVERS liberal fluids group protocol.

The 2016 SSC guidelines, which were developed jointly by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, likewise recommend that septic shock patients with hypotension initially receive at least 30 mL/kg of fluids (e.g., approximately 2.1 L for a 70-kg patient) within three hours (again, not 3 to 5 L within six hours, as prescribed by the CLOVERS liberal fluids group protocol) and that subsequent fluid should be administered for persistently hypotensive patients only as long as assessable hemodynamic factors continue to improve.<sup>19</sup> The 2016 SSC guidelines note, “We **do not** recommend therefore that fluid be given beyond initial resuscitation without some estimate of the likelihood that the patient will respond positively” [emphasis added]. The SSC guidelines state that during this resuscitative period, vasopressors should target a MAP of 65 mmHg (strong recommendation, moderate evidence) and do not specify a volume of fluid at which vasopressors should be considered and started. These guidelines are incompatible with the CLOVERS liberal fluids group protocol that stipulates continued administration of fluid alone if a subject is hypotensive until up to 5 L have been administered, while avoiding vasopressors unless very low blood pressures (SBP < 70

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<sup>15</sup> Self WH, Semler MW, Brown SM, et al. Liberal versus restrictive intravenous fluid therapy for early septic shock: Rationale for a randomized trial. *Ann Emerg Med*. 2018 May 9. pii: S0196-0644(18)30315-9. doi: 10.1016/j.annemergmed.2018.03.039. [Epub ahead of print]

<sup>16</sup> Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) protocol. Version II. November 17, 2017. [https://www.citizen.org/sites/default/files/clovers\\_protocol\\_versionii\\_111717\\_clean.pdf](https://www.citizen.org/sites/default/files/clovers_protocol_versionii_111717_clean.pdf). Accessed August 22, 2018.

<sup>17</sup> Centers for Medicare and Medicaid Services and The Joint Commission. *Specifications Manual for National Hospital Inpatient Quality Measures*. Discharges 01-01-18 (1Q18) through 06-30-18 (2Q18). Version 5.3.

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Accessed July 27, 2018.

<sup>18</sup> Centers for Medicare and Medicaid Services and The Joint Commission. *Specifications Manual for National Hospital Inpatient Quality Measures*. Discharges 07-01-18 (3Q18) through 12-31-18 (4Q18). Version 5.4.

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Accessed July 27, 2018.

<sup>19</sup> Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2017;45(3):486-552.

mmHg for 5 minutes) occur. Although the SSC guidelines have evolved from 2012<sup>20</sup> through 2018,<sup>21</sup> the SSC sepsis guideline bundles continued to recommend that patients with sepsis and/or hypotension (MAP <65 mmHg) and elevated lactate (>4 mmol/L) receive at least 30 mL/kg fluid bolus within three hours and vasopressors for persistent hypotension following that fluid bolus. Patients with persistent hypotension despite at least 30 mL/kg of fluid were also to have a volume and tissue perfusion assessment by six hours to guide further resuscitation.<sup>22</sup> Importantly, the 2018 update to the SSC guideline bundle recommends that patients presenting with sepsis and hypotension or lactate  $\geq$ 4 mmol/L receive 30 mL/kg of fluid within three hours but that vasopressors be started *during* this fluid administration if necessary to maintain MAP  $\geq$ 65 mmHg.<sup>23</sup>

Thus, in the CLOVERS liberal fluids group, the rapidity with which fluids initially are given, the avoidance of initiating vasopressors until 5 L of fluids have been administered in subjects with ongoing hypotension or hypoperfusion, and the level of hypotension allowed before administering vasopressors are inconsistent with both the U.S. government's SEP-1 performance measures and the recommendations of critical care society SSC guidelines. Fluid and vasopressor management in the CLOVERS liberal fluids group protocol deviates substantially from the usual-care guidelines in the SEP-1 performance measures and SSC guidelines and bundle.

### ***Evidence Cited in the CLOVERS Protocol to Support Claims About Septic Shock Management***

Finally, we examined whether the references cited by the investigators substantiate claims made in the CLOVERS protocol about the management of fluids and vasopressors during the usual care of patients with septic shock. Similar to the recently published report explaining the most current rationale for the CLOVERS trial,<sup>24</sup> the CLOVERS protocol asserts the following in its discussion of the rationale for the liberal fluids approach:<sup>25</sup>

A "liberal" fluid approach to septic shock management is characterized by the administration of several liters (> 30 mL/kg) of IV crystalloid to an adult during the initial resuscitation period and assumes intravascular volume expansion is more beneficial than other potential treatment approaches for hypotension. **Vasopressor medications are added if the patient is profoundly hypotensive (e.g. a systolic blood**

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<sup>20</sup> Dellinger RP, Levy MM, Rhodes A., et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med.* 2013;41(2):580-637.

<sup>21</sup> Levy MM, Evans L, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. *Intensive Care Med.* 2018;44(6):925-928.

<sup>22</sup> Dellinger RP, Levy MM, Rhodes A., et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med.* 2013;41(2):580-637

<sup>23</sup> Levy MM, Evans L, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. *Intensive Care Med.* 2018;44(6):925-928

<sup>24</sup> Self WH, Semler MW, Brown SM, et al. Liberal versus restrictive intravenous fluid therapy for early septic shock: Rationale for a randomized trial. *Ann Emerg Med.* 2018 May 9. pii: S0196-0644(18)30315-9. doi: 10.1016/j.annemergmed.2018.03.039. [Epub ahead of print].

<sup>25</sup> Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) protocol. Version II. November 17, 2017. [https://www.citizen.org/sites/default/files/clovers\\_protocol\\_versionii\\_111717\\_clean.pdf](https://www.citizen.org/sites/default/files/clovers_protocol_versionii_111717_clean.pdf). Accessed August 22, 2018.

**pressure < 70 mmHg) or remains hypotensive despite large volume fluid resuscitation.**

This liberal fluid approach is the predominant strategy used in U.S. emergency departments, and has been encouraged by the Surviving Sepsis Campaign Guidelines ([reference] 1), advocates of Early Goal Directed Therapy ([references] 2, 7, 8) and the National Quality Forum Severe Sepsis and Septic Shock Management Bundle (NQF #0500) ([reference] 9), which has been endorsed by Centers for Medicare and Medicaid Services (CMS) as the SEP-1 core measure ([reference] 12). [Emphasis added]

We examined the references cited in the above protocol excerpt to see whether any of them recommend, as components of usual care, treating adult sepsis patients initially with several liters of fluid and only initiating vasopressors if profound hypotension (SBP <70 mmHg) occurs or if hypotension persists despite large-volume resuscitation. CLOVERS protocol references 1 and 9 are the 2016 SSC guidelines<sup>26</sup> and the CMS SEP-1 performance measures,<sup>27,28</sup> respectively, and as noted above, they do not support the fluid and vasopressor management strategy that will be administered to subjects in the CLOVERS liberal fluids group.

CLOVERS protocol reference 2 is the Rivers et al early goal-directed therapy trial.<sup>29</sup> In that trial, the early goal-directed therapy group fluids were titrated to a target central venous pressure (CVP) (i.e., no set amount was given), and the actual volume that was given varied by up to 3 L (5.0±3.0 L total in the first six hours). With a CVP of 8 to 12 mmHg, vasopressors were administered for a MAP ≤65 mmHg.

CLOVERS protocol reference 7 was a single-center retrospective cohort study comparing the total early (zero to six hours) fluid administration in septic shock survivors (n=452) with that of non-survivors (n=142).<sup>30</sup> In the first three hours, survivors received a median total volume of 2.1 L (interquartile range [IQR] 0.9, 4.1) and non-survivors received 1.6 L (IQR 0.6, 3.0). In the second three hours, survivors received a median total volume of 0.7 L (IQR 0.3, 1.5) and non-survivors received 0.9 L (IQR 0.4, 1.7). Not only were the median volumes received by both groups of patients in the first three hours far less than 3 L, the combined median volumes over six hours were also less than 3.2 L in both groups and less than the minimum that would be administered to nearly all subjects in the CLOVERS liberal fluids group.

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<sup>26</sup> Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Crit Care Med.* 2017;45(3):486-552.

<sup>27</sup> Centers for Medicare and Medicaid Services and The Joint Commission. *Specifications Manual for National Hospital Inpatient Quality Measures*. Discharges 01-01-18 (1Q18) through 06-30-18 (2Q18). Version 5.3.

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[https://www.jointcommission.org/specifications\\_manual\\_for\\_national\\_hospital\\_inpatient\\_quality\\_measures.aspx](https://www.jointcommission.org/specifications_manual_for_national_hospital_inpatient_quality_measures.aspx).

Accessed July 27, 2018.

<sup>28</sup> Centers for Medicare and Medicaid Services and The Joint Commission. *Specifications Manual for National Hospital Inpatient Quality Measures*. Discharges 07-01-18 (3Q18) through 12-31-18 (4Q18). Version 5.4.

Downloaded from

[https://www.jointcommission.org/specifications\\_manual\\_for\\_national\\_hospital\\_inpatient\\_quality\\_measures.aspx](https://www.jointcommission.org/specifications_manual_for_national_hospital_inpatient_quality_measures.aspx).

Accessed July 27, 2018.

<sup>29</sup> Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345(19):1368-1377

<sup>30</sup> Lee SJ, Ramar K, Park JG, et al. Increased fluid administration in the first three hours of sepsis resuscitation is associated with reduced mortality: A retrospective cohort study. *Chest.* 2014;146(4):908-915

CLOVERS protocol reference 8 compared data from the Rivers et al early goal-directed therapy trial with the data from ProCESS, ARISE, and ProMISe.<sup>31</sup> The Rivers et al study presented the mean volumes of fluids from emergency department arrival time to six hours for control group subjects (3.5, 4.4, 4.3, and 4.0 L for the Rivers et al, ProCESS, ARISE, and ProMISe trials, respectively) but did not provide variability data (SDs or IQRs) that would have shown the wide distribution of volumes across subjects. Furthermore, as demonstrated above, many subjects in the usual-care groups in all three of the latter trials received less than 2 L of fluid from zero to six hours after randomization. Also, based on data from the ProMISe trial,<sup>32</sup> approximately 23 percent and 32 percent of septic shock subjects in the usual-care control group were receiving vasopressors at zero-to-one hours and one-to-two hours post-randomization, respectively, but only approximately 14 percent, 8 percent, and 6 percent had SBPs <70 mmHg at time zero hours, one hour, and two hours, respectively.<sup>33</sup>

Thus, we found in these references cited in the CLOVERS protocol no recommendations or data to support the claims made by the investigators that clinicians routinely wait until several liters of fluids are given and SBPs fall to <70 mmHg to treat sepsis patients with vasopressors. Based on the above references, such management would be unusual care.

### ***Risks of the CLOVERS Trial Design***

#### **Lack of a Usual-Care Control Group**

The CLOVERS investigators have designed a trial that compares two strategies of early care for septic shock, each of which differs fundamentally from the other but both of which differ substantially from usual care as described by the investigators' cited sources. One experimental group's strategy employs liberal fluids and restricted vasopressor use (liberal fluid group), whereas the other employs restricted fluids with liberal vasopressors (restrictive fluid group). The trial's lack of a usual-care control group precludes (1) appropriate monitoring to ensure the safety of enrolled human subjects and (2) drawing firm conclusions after the trial is completed that will actually improve and not worsen clinical practice for future patients.

Because septic shock is a potentially rapidly lethal clinical syndrome with a high mortality rate, if a new intervention being tested in a clinical trial is harmful, it will likely add to the organ failure and mortality that are part of the natural history of sepsis. However, without an adequate usual-care control group, it will be impossible to determine, as the trial progresses, whether one or both of the management strategies being studied is harmful (i.e., results in a higher mortality rate) compared with usual care. The protocol for each group restricts a different commonly employed sepsis therapy, and such deviations from usual care with the use of either strategy could increase the frequency of serious adverse events and death. Even if one group has a lower mortality rate than the other, both could still have a higher mortality rate compared with usual

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<sup>31</sup> Nguyen HB, Jaehne AK, Jayaprakash N, et al. Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe and ARISE. *Crit Care*. 2016 Jul 1;20(1):160. doi: 10.1186/s13054-016-1288-3.

<sup>32</sup> Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med*. 2015;372(14):1301-1311.

<sup>33</sup> Date was extrapolated from the figures. The estimated percentages of subjects with SBP <70 mmHg assumed that the data were independent and normally distributed.

care. If both strategies are harmful but neither is substantially different from the other, enrollment will continue and put more subjects at unnecessary risk, because the mortality rate in a usual-care control group will not be available to determine whether the trial should be stopped for harm.

Furthermore, in the absence of a usual-care control group, it is difficult to understand what conclusions can ultimately be drawn from CLOVERS that will guide potential modifications to improve usual-care practices for the early resuscitation of septic shock patients because the investigators are not studying usual care. It is evident that in either trial group, restricting the early use of one of the two major cardiovascular treatments for resuscitation of septic shock could worsen outcomes. Thus, one of the two experimental sepsis strategies may have a better survival rate than the other, but it will not be possible to determine whether it was also better (or worse) than current usual care. This trial design will only allow the conclusion that if the two treatment strategies studied are the only two therapeutic options allowed for septic shock (which is never the case), the strategy associated with the worse outcome should not be used. However, it cannot be concluded that the other strategy is the one that should be used because neither of the two “unusual-care” experimental strategies will have been compared with current usual care and shown to be equivalent to or better than usual care. Moreover, the conclusion of the trial could be to recommend a strategy that, although shown to be better than the other strategy, is actually more harmful than current usual care and, if adopted, will harm countless septic shock patients in perpetuity.

#### Misalignments Resulting from Failure to Account for Usual Care

In the view of the experts from whom we sought advice, in usual care for early sepsis it is widely recognized that therapy with either fluids or vasopressors can have adverse effects (for example, edema and ischemia) when used excessively and that each therapy can augment the effects of the other and limit the needed quantities of each. Thus, in usual care, clinicians do not routinely limit patients to predominantly fluids or vasopressors in the early stages to reverse septic shock. Rather, clinicians balance the use of each to maximize their benefits and limit their risks. Usual care of septic shock can be further characterized into the following three broad types, based on how fluid and vasopressor treatment changes as the sensitivity to these therapies decreases with increasing severity of the shock:

- (1) **Responsive to Fluid Only:** This is the mildest form of septic shock with minimal mortality, and these patients require variable amounts of fluids alone to be resuscitated. The rate and amount of fluids administered are normally adjusted based on the patient’s comorbidities, underlying volume status, and physiologic response to the fluid administration itself.
- (2) **Responsive to Fluid and Vasopressor Combined:** This is a moderately severe form of septic shock. These patients cannot be fully resuscitated with fluids alone, and vasopressors routinely are needed to treat persistent but reversible hypotension. However, once started on vasopressors, patients’ blood pressures are relatively easily managed with a constant or minimally adjusted rate of vasopressors and maintenance IV fluids.

- (3) **Inadequate Response to Fluid and Vasopressor Combined:** This is the severest and most lethal form of septic shock. These patients require increasing doses of both fluids and vasopressors. Despite both treatments, the blood pressure is persistently unstable, and increasing doses of both therapies are needed to manage resistant hypotension and organ hypoperfusion.

These progressively severe septic shock types and their increasingly intense treatments have been recognized by clinicians for at least the past 30 years and are reflected in the current nationally accepted algorithms recommended for sepsis treatment, such as the SSC guidelines<sup>34,35</sup> and CMS SEP-1 performance measures,<sup>36,37</sup> as presented above. Based on such algorithms, patients presenting with sepsis and hypotension are typically first treated with 0.5 to 3 L of total fluid in 0.5-1-L bolus doses, along with continuous maintenance fluid infusions. If hypotension resolves, no other specific hemodynamic therapy is recommended. If hypotension persists, vasopressors are started while the response to further fluids is assessed. Moderately ill patients frequently stabilize with this combination. But if these first two steps have been taken and hypotension persists, the treatments must be escalated based on physician judgment. Whether the best approach to the treatment of patients with this severe form of septic shock is either more fluids or more vasopressors is subject to debate. However, although CLOVERS includes this type of severely septic patient, it also will enroll many other patients with less severe cardiovascular instability who will stabilize with initial fluids alone or with fluids combined with vasopressors.

Not accounting for this patient-specific titrated usual care can result in dangerous “misalignments” of the two extreme interventions being tested in CLOVERS with the level of septic shock severity with which subjects randomly assigned to each experimental group will present.<sup>38,39</sup> Subjects with the mildest form of septic shock (type 1, **Responsive to Fluid Only**) who are randomly assigned to the CLOVERS restrictive fluid group may get vasopressors when they do not need them. Additional fluid administration, if monitored and titrated, would be more effective and safer than early vasopressor administration for treating this mild form of shock.

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<sup>34</sup> Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Crit Care Med.* 2017;45(3):486-552.

<sup>35</sup> Levy MM, Evans L, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. *Intensive Care Med.* 2018;44(6):925-928

<sup>36</sup> Centers for Medicare and Medicaid Services and The Joint Commission. *Specifications Manual for National Hospital Inpatient Quality Measures*. Discharges 01-01-18 (1Q18) through 06-30-18 (2Q18). Version 5.3. Downloaded from [https://www.jointcommission.org/specifications\\_manual\\_for\\_national\\_hospital\\_inpatient\\_quality\\_measures.aspx](https://www.jointcommission.org/specifications_manual_for_national_hospital_inpatient_quality_measures.aspx). Accessed July 27, 2018.

<sup>37</sup> Centers for Medicare and Medicaid Services and The Joint Commission. *Specifications Manual for National Hospital Inpatient Quality Measures*. Discharges 07-01-18 (3Q18) through 12-31-18 (4Q18). Version 5.4. Downloaded from [https://www.jointcommission.org/specifications\\_manual\\_for\\_national\\_hospital\\_inpatient\\_quality\\_measures.aspx](https://www.jointcommission.org/specifications_manual_for_national_hospital_inpatient_quality_measures.aspx). Accessed July 27, 2018.

<sup>38</sup> Deans KJ, Minneci P, Suffredini AF, et al. Randomization in clinical trials of titrated therapies: Unintended consequences of using fixed treatment protocols. *Crit Care Med.* 2007;35(6):1509-1516.

<sup>39</sup> Minneci PC, Eichacker PQ, Danner RL, et al. The importance of usual care control groups for safety monitoring and validity during critical care research. *Intensive Care Med.* 2008;34(5):942-947.

Starting vasopressors prematurely in patients who only need further fluids risks excessive vasoconstriction, maldistribution of blood flow, organ hypoperfusion, and worsened outcome.

For the subjects with moderate septic shock (type 2, **Responsive to Fluid and Vasopressors Combined**), the liberal fluids group and the restrictive fluids group each present different types of misalignments that result in different risks. First, such subjects randomized to the liberal fluids group may not receive vasopressors when needed for resuscitation, which risks delaying adequate perfusion to under-perfused organs. They also may receive additional fluids after intravascular volume repletion and when vasopressors are needed instead, which may produce tissue edema and organ hypoxia. Second, such subjects randomized to the restrictive fluids group may still be hypovolemic and not receive enough fluids for resuscitation, which also may risk delaying adequate perfusion to under-perfused organs. Giving vasopressors to a hypovolemic, hypotensive patient, potentially with the cardiac depression of sepsis, may increase tachycardia and hinder cardiac filling and also increase cardiac afterload, further depressing cardiac output and perfusion to essential organs. The non-judicious use of vasopressors also may cause ischemia to tissues due to excessive vasoconstriction.

Finally, similar to subjects with type 2 sepsis, the most severe septic shock patients (type 3, **Inadequate Response to Fluid and Vasopressors Combined**) who are randomly assigned to either group must progress to demonstrably poor physiologic outcomes (e.g., based on the CLOVERS protocol, evidence of fluid overload or extreme sustained hypotension in the liberal fluids group and evidence of severe hypotension or extreme hypovolemia in the restrictive fluids group) before they are eligible to receive fluids and vasopressors in combination. During usual care, physicians should and would attempt to prevent patients from developing these poor physiologic outcomes and preemptively treat with fluids and vasopressors together. Thus, many if not all type 3 patients face a similar risk of receiving predominantly either fluids or vasopressors when aggressive use of both therapies is necessary, resulting in inadequately perfused organs and an increased risk of organ failure and death.

Thus, when the variations in hemodynamic management that would occur during current usual care based on a patient's severity of sepsis are taken into account, there are clearly hazardous misalignments in treatment that will occur for many subjects receiving either of the two extreme experimental strategies CLOVERS is testing. For the type 1 sepsis subjects, because it is well-accepted that they do very well with fluids alone, there is no justification for randomly assigning them to the restrictive fluids group in which they will receive vasopressors unnecessarily. Likewise, it is well-accepted that type 2 patients also do very well following sufficient fluids combined with vasopressors, and it is not justified to withhold vasopressors and give these patients excessive amounts of fluid or to withhold fluids and give excessive amounts of vasopressors. For type 3 patients, the question that the CLOVERS investigators are asking (i.e., are fluids or vasopressors better for resuscitation early on in the most severe type of septic shock?) is irrelevant because both additional fluids and vasopressors in large amounts are often necessary to prevent rapid death.

Importantly, even the inclusion of a usual-care control group in CLOVERS would not address these perilous misalignments for subjects in the two experimental groups.

## ***Conclusion***

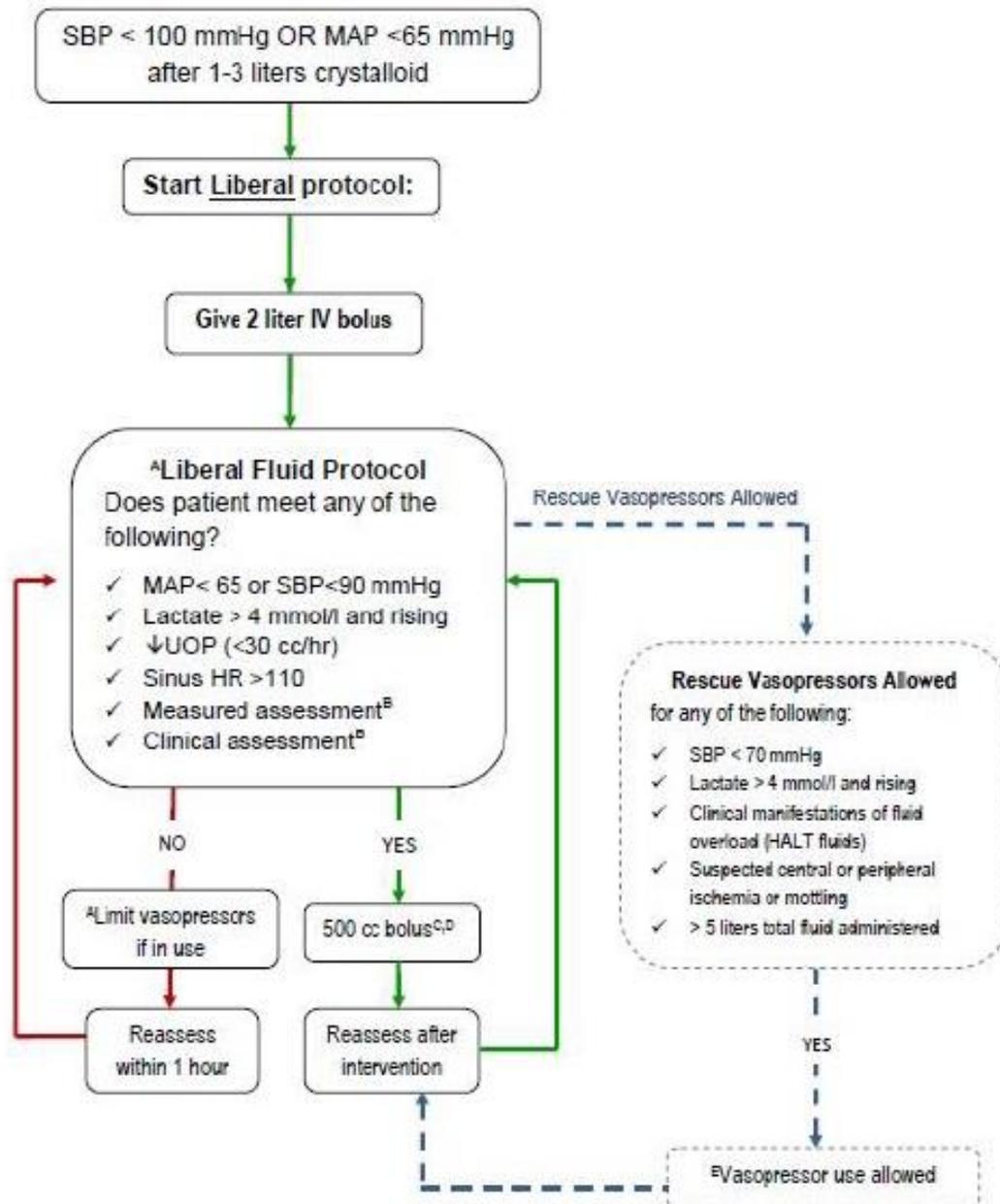
CLOVERS is enrolling subjects with septic shock who have a substantial mortality rate, and death is the primary outcome of interest. Based on the CLOVERS protocol, the investigators do not seem interested in studying — or even understanding — usual care. They have *not* performed a prospective observational study or a survey to ensure that the design of either of the two treatment strategies studied replicates the usual care administered in the hospitals enrolling patients. *Nor* are the investigators trying to describe or study in either group the recommendations for early septic shock treatment based on clinical practice guidelines or government-sponsored performance measures. The investigators also are *not* trying to develop a protocol that is representative of usual care for either group based on the available scientific literature worldwide.

The CLOVERS design does not comport with typical trial designs that aim to gain knowledge to improve the clinical care of patients. It is not a pragmatic trial because neither strategy is consistent with usual care. Nor is it comparative effectiveness research, because such trials compare two currently used interventions or one usual-care intervention with an experimental one. The design of CLOVERS cannot do the work of a randomized *controlled* trial that seeks to learn how to improve clinical care because neither strategy being tested represents current practice for sepsis management.

This trial is most analogous to a physiologic study where two opposing interventions have been designed to determine the outcome of using one treatment strategy compared with the other. Scientists may learn something about physiologic responses of seriously ill patients, but the subjects enrolled in the study are being used as mere means to that end. CLOVERS cannot provide information relevant to improving the current usual care of patients with sepsis. A serious ethical problem with its trial design is that it places seriously ill patients at risk without the possibility of gaining information that can provide benefits either to the subjects or to future patients with sepsis. In sum, no firm conclusions can be drawn from the results of this trial that would improve usual care for septic shock.

## Appendix

## A.1 Liberal Protocol (follow for 24 hours)



<sup>A</sup> If Patient is on vasopressors – titrate down/off vasopressors as feasible

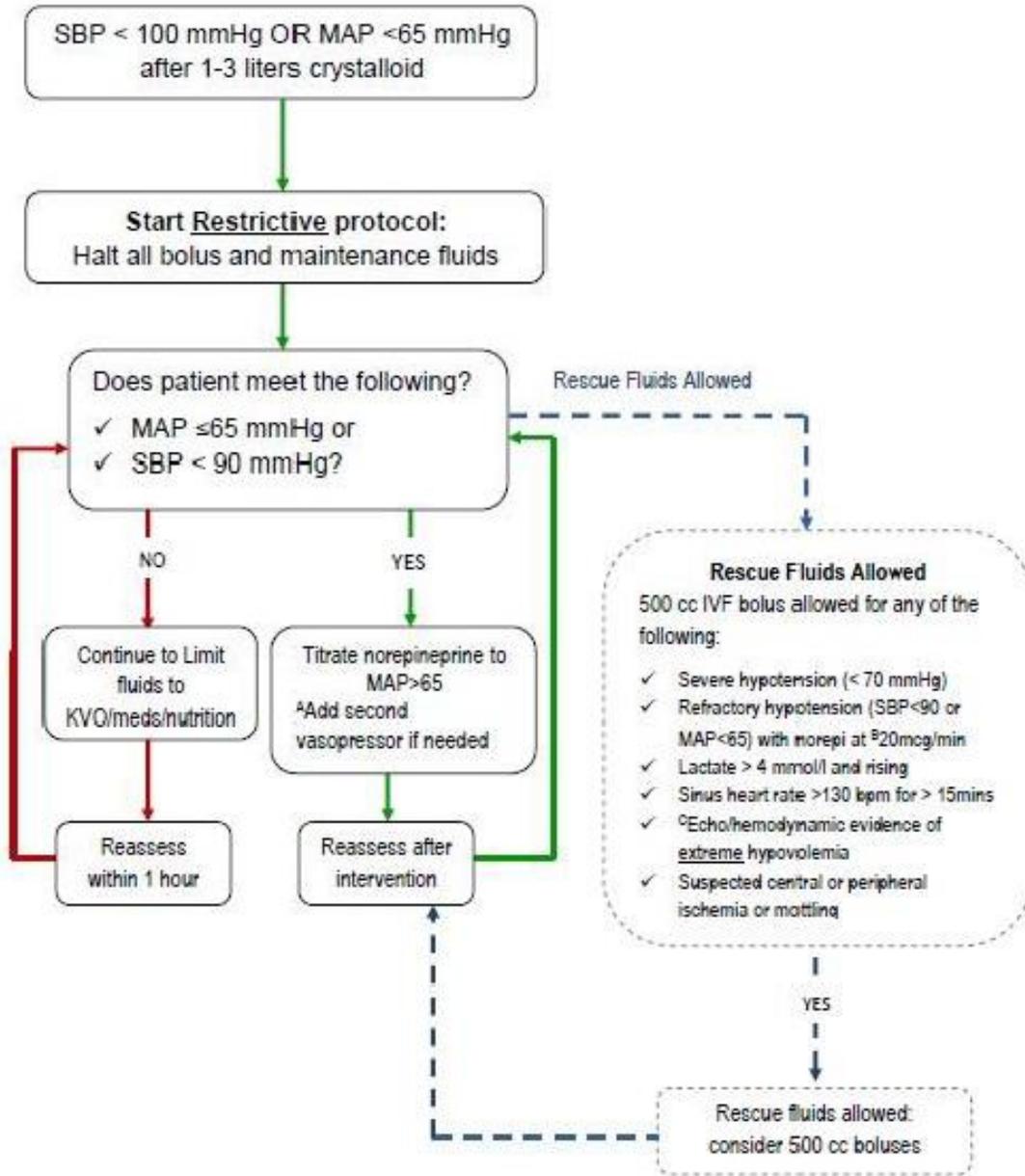
<sup>B</sup> Any measured/clinical assessment of volume status or volume responsiveness (e.g. echo, IVC measurement, CVP, etc) suggesting benefit from additional fluid

<sup>C</sup> HALT fluids for clinical manifestations of fluid overload

<sup>D</sup> Vasopressors allowed after 5L total administered

<sup>E</sup> Norepinephrine as preferred primary vasopressors; may add a second vasopressor once a dose > 20 mcg/min or 0.25 mcg/kg/min is reached

**A.2 Restrictive Protocol (follow for 24 hours)**



<sup>A</sup>Epinephrine suggested, but not mandated, as second vasopressor

<sup>B</sup>Norepinephrine 20mcg/min or 0.25 mcg/kg/min

<sup>C</sup>Defined as: maximal IVC diameter < 5mm; or Empty left ventricle on echo (e.g. left-ventricular end-diastolic area index < 5.5 cm<sup>2</sup>/m<sup>2</sup> BSA) or Substantial volume responsiveness defined as stroke volume increase > 30% in response to a passive leg raise, fluid challenge, or positive pressure breaths

**Enclosure B: Brief biographic summaries  
and Web links to complete curricula vitae of  
experts who advised Public Citizen**

### **Brief Biographic Summary – Charles Natanson, M.D.**

Dr. Charles Natanson received his medical degree from Columbia University College of Physicians and Surgeons and did a residency in Internal Medicine at The New York Hospital-Cornell Medical Center and in Anesthesia at the University of California San Francisco. He has four board certifications: Internal Medicine, Anesthesia, Critical Care Medicine, and Critical Care Anesthesia. He is a Senior Investigator and Chief of the Anesthesia Section in the Critical Care Medicine Department at the National Institutes of Health (NIH) Clinical Center in Bethesda, MD. He also holds the following hospital appointments: Clinical Professor of Medicine, George Washington University; Professor of Anesthesia, University of Maryland; and Assistant Professor of Anesthesia, Johns Hopkins University. Early in his research career he won the Young Investigator Award from the American Federation for Clinical Research for his work at NIH on the cardiovascular abnormalities of septic shock and was also elected to the American Society for Clinical Investigation. He has published over 200 peer-reviewed papers on the cardiovascular abnormalities of septic shock, new treatment strategies for septic shock, and the pathophysiology of septic shock. More recently, he has published more than a dozen peer-reviewed papers on protecting subjects in usual-care clinical trials. For more than 35 years and presently, he has been a full-time attending in the Critical Care Medicine Department at the NIH and taken care of thousands of critically ill patients; predominantly cancer, collagen vascular disease, and immune-deficient patients with septic shock. He has lectured all over the world on septic shock and safety in clinical trials and has been an unpaid consultant as part of his official duties at NIH to industry, the Food and Drug Administration, and the Office for Human Research Protections.

View Dr. Natanson complete curriculum vitae at  
[https://www.citizen.org/sites/default/files/natanson\\_charles-cv\\_8-13-2018.pdf](https://www.citizen.org/sites/default/files/natanson_charles-cv_8-13-2018.pdf)

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### **Brief Biographic Summary – Peter Q. Eichacker, M.D.**

Dr. Peter Q. Eichacker received his medical degree from New York University and did a residency and chief residency in Internal Medicine followed by a fellowship in Pulmonary Medicine at the Albert Einstein College of Medicine and Bronx Municipal Hospital Center. He then completed a fellowship in Critical Care Medicine at the National Institutes of Health (NIH) Clinical Center in Bethesda, MD. He has been board certified in Internal, Pulmonary and Critical Care Medicine for 30 or more years. He is Senior Investigator and Head of the Critical Care Medicine Section in the Critical Care Medicine Department at the NIH Clinical Center. For the past 30 years his research has focused on the pathogenesis and management of sepsis and septic shock. He has published over 150 peer reviewed papers, chapters and editorials having to do with sepsis and critical care medicine and the conduct of clinical trials in these areas. His clinical work in the Critical Care Medicine Department at the NIH Clinical Center has included the care of many patients with complex underlying conditions that have been complicated by the development of sepsis and septic shock. He has lectured nationally and internationally on the subject of sepsis and septic shock and has been a consultant to the Food and Drug Administration and to the Centers for Disease Control and Prevention on these subjects.

View Dr. Eichacker complete curriculum vitae  
at [https://www.citizen.org/sites/default/files/curriculum\\_vitae-pqeallab\\_02-26-18.pdf](https://www.citizen.org/sites/default/files/curriculum_vitae-pqeallab_02-26-18.pdf)

**Enclosure C: List of PETAL Network  
Institutions Identified on the  
ClinicalTrials.gov Website as Study  
Locations for CLOVERS**

**List of PETAL Network Institutions Identified on the ClinicalTrials.gov Website  
as Study Locations for CLOVERS (Last Updated May 28, 2018)<sup>1</sup>**

**California**

Ronald Reagan UCLA, Los Angeles  
Stanford University Hospital, Stanford (not yet recruiting subjects)  
UCSF Fresno, Fresno  
UCSF San Francisco, San Francisco

**Colorado**

Denver Health Medical Center, Denver  
St. Joseph Hospital, Denver (not yet recruiting subjects)  
University of Colorado Hospital, Aurora

**Illinois**

Northwestern University, Evanston (not yet recruiting subjects)

**Indiana**

Indiana University Health Methodist Hospital, Indianapolis

**Kentucky**

University of Kentucky, Lexington (not yet recruiting subjects)

**Louisiana**

University Medical Center (LSU), New Orleans (not yet recruiting subjects)

**Maine**

Maine Medical Center, Portland (not yet recruiting subjects)

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<sup>1</sup> U.S. National Library of Medicine. ClinicalTrials.gov. Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS). Updated May 28, 2018. <https://clinicaltrials.gov/ct2/show/study/NCT03434028>. Accessed August 22, 2018.

## **Massachusetts**

Beth Israel Medical Center, Boston  
Baystate Medical Center, Springfield  
Brigham and Women's Hospital, Boston (not yet recruiting subjects)  
Massachusetts General Hospital, Boston (Coordinating Site) (not yet recruiting subjects)  
St. Vincent Hospital, Worcester (not yet recruiting subjects)

## **Michigan**

Henry Ford Medical Center, Detroit (not yet recruiting subjects)  
University of Michigan Medical Center, Ann Arbor

## **Mississippi**

University of Mississippi Medical Center, Jackson (not yet recruiting subjects)

## **New York**

Montefiore Medical Center, New York  
Mt. Sinai Hospital, New York (not yet recruiting subjects)

## **North Carolina**

Duke University Medical Center, Durham (not yet recruiting subjects)  
University of North Carolina at Chapel Hill, Chapel Hill (not yet recruiting subjects)  
Wake Forest Baptist Health, Winston-Salem

## **Ohio**

Cleveland Clinic Foundation, Cleveland  
Ohio State University Wexner Medical Center, Columbus  
University of Cincinnati Medical Center, Cincinnati (not yet recruiting subjects)

## **Oregon**

Oregon Health and Science University OHSU, Portland (not yet recruiting subjects)

## **Pennsylvania**

Penn State Hershey Medical Center, Hershey (not yet recruiting subjects)  
UPMC Mercy, Pittsburgh (not yet recruiting subjects)  
UPMC Presbyterian, Pittsburgh (not yet recruiting subjects)  
UPMC Shadyside, Pittsburgh (not yet recruiting subjects)

**Tennessee**

Vanderbilt University Medical Center

**Utah**

Intermountain Medical Center, Murray

LDS Hospital, Salt Lake City (not yet recruiting subjects)

McKay-Dee Hospital, Ogden (not yet recruiting subjects)

University of Utah Health Sciences Center, Salt Lake City (not yet recruiting subjects)

Utah Valley Regional Medical Center, Provo (not yet recruiting subjects)

**Virginia**

University Virginia Medical Center, Charlottesville (not yet recruiting subjects)

VCU Medical Center, Richmond (not yet recruiting subjects)

**Washington**

Harborview Medical Center, Seattle

Swedish Hospital First Hill, Seattle (not yet recruiting subjects)

University of Washington Medical Center, Seattle (not yet recruiting subjects)