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April 29, 2019

The Honorable Daniel R. Levinson
Inspector General
U.S. Department of Health and Human Services
330 Independence Avenue SW
Washington, DC 20201

RE: NIH Leadership Forbids NIH Sepsis Experts from Communicating with OHRP Regarding Allegations of Serious Ethical and Regulatory Lapses in an NIH-Funded Sepsis Clinical Trial

Dear Inspector General Levinson:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, respectfully requests that your office immediately launch a formal investigation to scrutinize the conduct of senior National Institutes of Health (NIH) officials, including Principal Deputy Director Lawrence A. Tabak, who, according to an article published by *The Wall Street Journal* (*WSJ*) on April 28,[1] explicitly forbade two senior scientists at the NIH Clinical Center from communicating with the Office for Human Research Protections (OHRP) about alleged serious ethical and regulatory lapses involving the ongoing NIH-funded Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis **(**CLOVERS) trial, despite a direct request from OHRP to interview these scientists about these issues.

As you are aware, the OHRP is the regulatory agency charged with implementing and enforcing the U.S. Department of Health and Human Services (HHS) human subjects protection regulations (45 C.F.R. Part 46). Among the agency's core responsibilities is to conduct compliance oversight evaluations of substantive allegations of noncompliance with these regulations that involve research funded by the NIH and other HHS agencies.

The reported efforts by the NIH leadership to muzzle its own scientific experts and thereby effectively interfere in the OHRP's compliance oversight evaluation of the alleged ethical and regulatory lapses of the CLOVERS trial constitute gross misconduct and corruption at the highest levels of the NIH.

[1] Burton TM. NIH blocks two doctors from speaking out to investigators. *The Wall Street Journal*. April 28, 2019. https://www.wsj.com/articles/nih-blocks-two-doctors-from-speaking-out-to-investigators-11556456520. Accessed April 29, 2019.

Overview of CLOVERS and ethical and regulatory lapses

CLOVERS is a multicenter, randomized, unblinded, two-arm clinical trial being conducted by a group of academic hospitals called the NIH-funded Prevention and Early Treatment of Acute Lung Injury (PETAL) Network.[2] The trial, which was opened to enrollment in March 2018, involves 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 experimental 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 strategy), whereas subjects in the other group receive a management strategy that employs restricted IV fluid administration with liberal use of vasopressors (restrictive fluids strategy).[3] 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.

On August 28, 2018, Public Citizen submitted a detailed written complaint to the OHRP about CLOVERS and requested that the agency conduct a compliance oversight investigation of the trial and its review and approval by the responsible institutional review board(s).[4] Based on our review of the then-current version of the protocol, sample consent form, and relevant background scientific literature, we concluded that the trial fails to (a) materially comply with key requirements of 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 were based on a critical analysis of the trial's design that was enclosed with our letter to the OHRP. 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 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. They 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 (the enclosure provides their brief biographic summaries and web links to their complete curricula vitae).

It is our understanding that OHRP, in evaluating our complaint, has sought input from Drs. Natanson and Eichacker regarding the adequacy of revisions to the CLOVERS protocol that were made subsequent to our complaint to OHRP.

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[2] PETAL Network: Prevention & Early Treatment of Acute Lung Injury. http://petalnet.org/. Accessed April 29, 2019.

[3] 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. Accessed April 29, 2019.

[4] Public Citizen. Complaint letter to the Office for Human Research Protections regarding CLOVERS. https://www.citizen.org/sites/default/files/2446.pdf. Accessed April 29, 2019.

Disclosures of improper conduct by senior NIH officials

Based on documents obtained from the NIH and multiple interviews — including one with Dr. Tabak, the top deputy to NIH Director Francis Collins — the *WSJ* yesterday reported the disturbing revelation that senior NIH officials, including Dr. Tabak, explicitly forbade Drs. Natanson and Eichacker from communicating with the OHRP about the ethical and regulatory lapses in CLOVERS that were described in our August 2018 letter to the regulatory agency. The following are key excerpts from the *WSJ* article that detail the troubling conduct of senior NIH officials involved in this matter:

> The National Institutes of Health, the U.S. government's premier health research agency, is refusing to allow two of its doctors to respond to government investigators looking into the quality of a continuing clinical trial of new blood-infection treatments on thousands of patients, according to NIH documents and multiple interviews.
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> The resulting tensions within the NIH have pitted the office of the agency's director, Francis Collins, against an internal NIH committee of 24 scientists, who are raising questions over the freedom researchers are afforded to critique the work of colleagues. That freedom has long been a crucial form of quality control in the safe development of new medicines and therapies. Barring doctors from commenting on a safety inquiry curtails that freedom, the committee contends.
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> The NIH director's office maintains that the decision to keep the researchers from talking with investigators concerns choosing the right people to speak for the organization, not scientists' freedom to critique.
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> Behind the standoff is a multiyear clinical trial to be completed in 2021, a test of new procedures to treat the often-lethal bloodstream infection known as sepsis, which affects more than a million Americans each year. The trial, funded by the NIH, is known as the Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis trial, or Clovers, and involves testing two treatment approaches on some 2,320 patients…
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> At the center of the clash are two NIH doctors, Charles Natanson and Peter Eichacker, both of whom have published frequently on the topic of sepsis, medical research and critical-care medicine. Last year, they raised concerns about the way the sepsis study was being conducted, resulting in a critical report on the trial by the nonpartisan consumer group Public Citizen. The group said the Clovers study "predictably will expose many subjects to dangerous deviations from critical care."
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> That publication caught the attention of the Office for Human Research Protections, a federal agency mandated with assuring American patients aren't harmed in clinical research. **The OHRP launched a federal review of the conduct of the clinical trial, and sought to interview Drs. Natanson and Eichacker.**
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> **NIH Director Collins's top assistant, Principal Deputy Director Lawrence A. Tabak, confirmed he prohibited the two doctors from answering questions from OHRP investigators.**

> The Council of the Assembly of Scientists, an internal NIH committee of 24 doctors and researchers representing the scientists on the NIH campus, wrote in a memo to Dr. Tabak that **they were "extremely concerned" that the two doctors "have been forbidden by NIH leadership to respond to OHRP, either as an official duty activity or an outside activity."**
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> Dr. Collins, the NIH director who is also a well-known geneticist, declined to comment. His assistant, **Dr. Tabak, who ordered the blocking of the two doctors' testimony, said: "The agency has the responsibility to choose people to respond on behalf of the NIH. This has nothing to do with freedom of speech." He said Dr. Collins was aware of the decision…**
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> The Clovers trial continues, encompassing about 50 hospitals, although the protocol for the study has changed somewhat. **The two doctors are still troubled by the study methodology making it more imperative they speak with OHRP officials**, people familiar with the issue say…
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> The issue came to a head two months ago around an NIH conference table, with a half-dozen of the 24 senior scientists and senior NIH officials, including Dr. Tabak, convening to discuss the underlying issues like research freedom of speech. **Dr. Tabak repeatedly contended that Dr. Natanson's and Dr. Eichacker's actions and commentary were inappropriate, according to people present at the meeting**.[5]
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> [Emphasis added]

The efforts by NIH senior officials, as described by the *WSJ*, to muzzle their own scientific experts and thereby effectively interfere in the OHRP's compliance oversight evaluation of the alleged serious ethical and regulatory lapses involving CLOVERS constitute gross misconduct and corruption at the highest levels of the NIH, tantamount to an obstruction of ethical justice for the subjects of the CLOVERS trial. Such misconduct demonstrates that senior NIH officials are more interested in protecting the organization from public criticism and avoiding potential embarrassment than in protecting the rights and welfare of human subjects.

As you may know, the OHRP — formerly the Office for Protection from Research Risks (OPRR) in the NIH Office of the Director — was administratively relocated from NIH to the HHS Office of the Secretary in large part because of the conflicts of interest that existed between NIH, the largest federal funder of human subjects research, and OPRR. Consistent with the purpose of that relocation, NIH must have no role in determining with whom OHRP staff speak when conducting compliance oversight evaluations of NIH-funded research.

As the HHS Inspector General, you yourself must recognize the importance of ensuring that all NIH employees who have concerns about ethical or regulatory violations related to the protection of human subjects in any NIH-funded (or other) clinical trial are free to communicate

[5] Burton TM. NIH blocks two doctors from speaking out to investigators. *The Wall Street Journal*. April 28, 2019. https://www.wsj.com/articles/nih-blocks-two-doctors-from-speaking-out-to-investigators-11556456520. Accessed April 29, 2019.

with the OHRP about those concerns without fear of reprisal. Likewise, with respect to any NIH-funded research, NIH employees must feel empowered to contact — without fear of retaliation — the Office of Research Integrity about concerns regarding scientific misconduct, the Food and Drug Administration about concerns regarding the use of investigational drugs and medical devices, and your office about concerns regarding fraudulent use of NIH funds.

The actions of the NIH leadership to prohibit such communications with OHRP undermine the protections for human subjects who are enrolled in NIH-funded research and, ultimately, public trust in NIH. Restoring that trust will require a change in leadership at NIH.

Conclusions and requested actions

We urge the HHS Office of Inspector General (OIG) to immediately launch a formal investigation into the matters described in the *WSJ* article. Given that the improper conduct described in the article involved the most senior staff within the NIH Office of the Director, it is essential that the OIG not defer any part of the investigation of this matter to the Office of Management Assessment, which reports directly to the NIH Director.

The investigation should address the following important questions, among others:

(1) Besides Dr. Tabak, who were the other NIH officials involved in the decision to forbid Drs. Natanson and Eichacker from communicating with the OHRP regarding their concerns about CLOVERS? What role did Dr. Collins play in making it? Who, of those involved, opposed the decision?

(2) What were the actual motives of the senior NIH officials for their decision?

(3) With what adverse actions were Drs. Natanson and Eichacker threatened if they communicated further with the OHRP about CLOVERS?

We hope you share our concern regarding this troubling matter, and we look forward to an appropriate, favorable response to our urgent request. 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

cc: The Honorable Alex Azar, U.S. Secretary of Health and Human Services
ADM Brett P. Giroir, M.D., Assistant Secretary for Health, HHS

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

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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
athttps://www.citizen.org/sites/default/files/curriculum_vitae-pqeallab_02-26-18.pdf