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October 29, 2018

Scott Gottlieb, M.D.
Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

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: Hennepin County Medical Center’s failure to protect human subjects enrolled in prospective clinical trials comparing the safety and effectiveness of ketamine with those of other drugs for management of agitation and other high-risk clinical trials

Dear Drs. Gottlieb and Menikoff:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, and the undersigned individuals are writing in follow-up to our July 25, 2018, letter¹ — which was cosigned by 62 other individuals with expertise spanning, among other things, bioethics, medicine, human subjects protections, human rights, and law — urging the Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP) to immediately launch formal compliance oversight investigations into the conduct and oversight of two prospective clinical trials that involved testing the safety and effectiveness of the general anesthetic ketamine in comparison with those of other potent sedative drugs for management of prehospital agitation (the ketamine clinical trials) without the human subjects’ consent.

Our July 25 letter explained how these ketamine clinical trials — which were conducted by investigators at the Hennepin County Medical Center (HCMC) in Minneapolis, MN — failed to (a) materially comply with key requirements of FDA and Department of Health and Human Services (HHS) regulations for the protection of human subjects at 21 C.F.R. Parts 50 and 56 and at 45 C.F.R. Part 46, respectively, and (b) satisfy the basic ethical principles upon which those regulations are founded. Disturbingly, the clinical trials were incorrectly determined by the

¹ Public Citizen et al. Letter to the Food and Drug Administration and the Office for Human Research Protections. July 25, 2018. <https://www.citizen.org/sites/default/files/2442.pdf>. Accessed October 25, 2018.

investigators and the HCMC's institutional review board (IRB) to involve no more than minimal risk to the subjects and, based on that determination, the IRB waived the informed consent requirements under HHS regulations at 45 C.F.R. § 46.116(d), when in fact these experiments clearly involved research-stipulated interventions that far exceeded the minimal risk threshold.

We obtained under the Freedom of Information Act a copy of the Form FDA 483, Inspectional Observations (483 form) for the FDA's August 7-23, 2018, inspection of the HCMC's IRB, which is called the Human Subjects Research Committee (copy enclosed). The observations described in the 483 form confirm our previous contention that there were unacceptable regulatory and ethical lapses in the oversight and conduct of at least one of the two ketamine clinical trials referenced in our July 25 letter, as well as other clinical trials reviewed and approved by the HCMC's IRB. In particular, the FDA inspectors made the following observations:

- (1) The IRB approved the conduct of research but did not determine that informed consent would be sought from each prospective subject or the subject's legally authorized representative to the extent required by FDA human subjects protection regulations at 21 C.F.R. Part 50. Specifically, the IRB approved studies for waiver of informed consent under HHS human subjects protection regulations at 45 C.F.R. 46.116 without determining the informed consent requirements of FDA regulations at 21 C.F.R. Part 50, and these studies do not appear to meet the criteria for the exception from the general informed consent requirements under FDA regulations at 21 C.F.R. 50.23 or the exception from informed consent requirements for emergency research under FDA regulations at 21 C.F.R. 50.24.
- (2) The IRB approved the conduct of research in situations where some or all of the subjects were likely to be vulnerable to coercion or undue influence, but it did not determine that additional safeguards had been included in the study to protect the rights and welfare of those subjects. Specifically, the IRB has approved studies that are identified as including a Vulnerable Subjects category (i.e., "impaired ability to give informed consent") without evidence of determining that additional safeguards had been included in the study to protect the rights and welfare of those subjects.

For each of these observations, the FDA inspectors cited four examples of clinical trials, the first of which was titled *Ketamine vs. Haloperidol for Severe Agitation in the Prehospital Setting*, one of the two ketamine clinical trials described in our July 25 letter. The titles and IRB numbers for two of the cited clinical trials were redacted from the 483 form; one of these may have been the second ketamine clinical trial described in our July 25 letter (*Ketamine versus Midazolam Trial for Prehospital Agitation*) that was suspended by the HCMC on June 25, 2018, a date that matches the "Paused" date for the second example cited on the 483 form.

The fourth example, *Prospective Observational Investigation of Olanzapine versus Haloperidol versus Ziprasidone versus Midazolam for the Treatment of Acute Undifferentiated Agitation in the Emergency Department* (IRB #17-4345; ClinicalTrials.gov identifier NCT03211897), was another high-risk, prospective nonrandomized clinical trial that tested the comparative safety and effectiveness of olanzapine, haloperidol, ziprasidone, and midazolam for management of acutely

agitated patients in the emergency department setting. As with the two ketamine clinical trials described in our July 25 letter, which of these four drugs that the human subjects received was automatically determined by the time period in which the subjects were enrolled, not by the individual clinical judgment of the health care professionals caring for each subject.

Astonishingly, the researchers who conducted this trial initially sought to conduct it using a randomized, double-blind design and with an exception from the informed consent requirements for emergency research under FDA regulations at 21 C.F.R. 50.24, but, according to the researchers, the FDA refused to approve the investigational new drug application required for the trial under the provisions of the exception because the agency determined that “there was insufficient evidence that this [subject] population could not provide informed consent.”²

A stunning new revelation documented in the FDA’s 483 form is that high-risk clinical trials involving highly vulnerable subjects, including at least one of the ketamine clinical trials and IRB study #17-4345, have been too hastily reviewed and approved by the HCMC’s IRB under an expedited review procedure, which is only permitted for certain categories of research that involve no more than minimal risk and, therefore, was not appropriate for these high-risk ketamine clinical trials or IRB study #17-4345. As you are aware, under an expedited review procedure, only the IRB chairperson (or one or more members designated by the chairperson) reviews and approves the research.

We commend the FDA for taking our July 25 complaint seriously and promptly conducting an inspection of the HCMC’s IRB. The observations in the FDA’s 483 form confirm our previous assessment that there have been serious systemic breakdowns in the HCMC’s human subjects protection program. The medical center’s IRB appears to lack even a basic understanding of federal regulations for the protection of human subjects and is clearly incapable of fulfilling its obligation to protect the rights and welfare of human subjects.

Therefore, if they have not already done so, it is imperative that the FDA and OHRP immediately take the following steps to ensure the protection of human subjects who would otherwise be endangered by participating in high-risk research at the HCMC:

- (1) Suspend the registration of the HCMC’s IRB until the actions described in (3)(b) below are taken.
- (2) Suspend approval of the HCMC’s Federalwide Assurance — the written document in which the medical center committed to the HHS that it would comply with all applicable federal regulations for the protection of human subjects, a commitment that the HCMC has not fulfilled — until the actions described in (3)(b) below are taken.
- (3) Direct the HCMC to take the following actions:

² Klein LR, Driver BE, Miner JR, et al. Intramuscular midazolam, olanzapine, ziprasidone, or haloperidol for treating acute agitation in the emergency department. *Ann Emerg Med.* 2018;72(4):374-385.

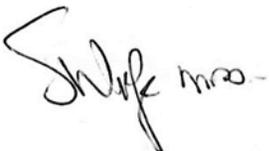
- (a) Immediately suspend all ongoing human subjects research, except where it is in the best interests of individual human subjects to continue participation in research; any such exceptions should be reported to the FDA and OHRP.
 - (b) Reconstitute and train one or more new IRBs.
 - (c) Retrain all HCMC researchers involved in the conduct of human subjects research.
 - (d) Require that each suspended research project, before it is allowed to resume, be reevaluated by the newly constituted and trained IRB to determine whether (i) it had an appropriate level of review and satisfied all criteria required for approval and (ii) any waiver of the requirements to obtain and document the informed consent of the human subjects satisfied all criteria required for such waivers.
 - (e) Develop a plan to inform each subject whose rights were violated by being enrolled in any clinical trial without appropriate informed consent, including the two ketamine clinical trials, about their participation in the research, the nature of the regulatory and ethical lapses that occurred, and the steps that the HCMC has or will take to redress these violations.
- (4) Restrict the HCMC's use of the expedited IRB review procedure until the IRB has demonstrated the ability to appropriately review research at convened IRB meetings and to correctly identify research that is eligible for expedited review.

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

Public Citizen

October 29, 2018, Letter to FDA and OHRP Regarding
Hennepin County Medical Center

A handwritten signature in black ink, appearing to read 'Carl Elliott', written in a cursive style.

Carl Elliott, M.D. Ph.D.
Professor, Center for Bioethics
University of Minnesota

A handwritten signature in black ink, appearing to read 'Leigh Turner', written in a cursive style.

Leigh Turner, Ph.D.
Associate Professor, Center for Bioethics
University of Minnesota
Enclosure

cc: Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 250 Marquette Ave, Ste. 600 Minneapolis, MN 55401 (612)334-4100 Fax:(612)334-4134	DATE(S) OF INSPECTION 8/7/2018-8/23/2018*
	FEI NUMBER 2127118

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Craig J. Peine, M.D., IRB Chair

FIRM NAME Human Subjects Research Committee	STREET ADDRESS Hennepin County Medical Center, , Hennepin Healthcare System, Inc.;914 S 8
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CITY, STATE, ZIP CODE, COUNTRY Minneapolis, MN 55404-1204	TYPE ESTABLISHMENT INSPECTED Institutional Review Board
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This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

The IRB approved the conduct of research, but did not determine that informed consent would be sought from each prospective subject or the subject's legally authorized representative, to the extent required by 21 CFR 50.

Specifically, the IRB approved studies for waiver of consent under 45 CFR 46.116 without determining the informed consent requirements of 21 CFR 50; and, that do not appear to meet the criteria for exception from informed consent (21 CFR 50.23) nor emergency research (21 CFR 50.24). Examples:

IRB#	Study title	Approval date	Review type	Study status
14-3841	Ketamine vs. Haloperidol for Severe Agitation in the Prehospital Setting	7/10/2014	Expedited	Closed 7/1/2016
(b) (4)	(b) (4)	5/11/2017	Expedited	Paused 6/25/2018
17-4345	Prospective Observational Investigation of Olanzapine versus Haloperidol versus Ziprasidone versus Midazolam for the Treatment of Acute Undifferentiated Agitation in the Emergency Department	5/22/2017	Expedited	Closed 5/1/2018
(b) (4)	(b) (4)	5/29/2018	Expedited	Paused 7/16/2018

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Sharon L Matson, Investigator Kellie L Thommes, Investigator	Sharon L Matson Investigator Signed By: Sharon L Matson -S Date Signed: 08-23-2018 10:40:44 X _____	DATE ISSUED 8/23/2018

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

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	(b) (4)			
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OBSERVATION 2

The IRB approved the conduct of research in a situation where some or all of the subjects were likely to be vulnerable to coercion or undue influence, but did not determine that additional safeguards had been included in the study to protect the rights and welfare of those subjects.

Specifically, the IRB has approved studies that are identified as including a Vulnerable Subjects category "impaired ability to give informed consent" without evidence of determining additional safeguards had been included in the study to protect the rights and welfare of those subjects. Examples are noted above under Observation 1.

OBSERVATION 3

The IRB used an expedited review procedure for research which did not appear in an FDA list of categories eligible for expedited review, and which had not previously been approved by the IRB.

Specifically, requests that do not meet the criteria for expedited review have been given expedited approval. Examples:

A. Requests for emergency use (EU) of experimental or investigational products:

IRB#	Product requested	FDA#	EU request date	Approval date	Date of use	Report date
(b) (4)	(b) (4)	(b) (4)	6/2/2017	6/2/2017	Not used	6/9/2017
(b) (4)	(b) (4)	(b) (4)	9/1/2017	9/1/2017	(b) (6)	9/12/2017
(b) (4)	(b) (4)	(b) (4)	11/6/2017	11/6/2017	(b) (6)	12/1/2017

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Sharon L Matson, Investigator Kellie L Thommes, Investigator	DATE ISSUED 8/23/2018
	Sharon L Matson Investigator Signed By: Sharon L Matson -S Date Signed: 08-23-2018 10:48:44 X _____	

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

<small>DISTRICT ADDRESS AND PHONE NUMBER</small> 250 Marquette Ave, Ste. 600 Minneapolis, MN 55401 (612)334-4100 Fax: (612)334-4134	<small>DATE(S) OF INSPECTION</small> 8/7/2018-8/23/2018*
	<small>FEI NUMBER</small> 2127118

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
 Craig J. Peine, M.D., IRB Chair

<small>FIRM NAME</small> Human Subjects Research Committee	<small>STREET ADDRESS</small> Hennepin County Medical Center, , Hennepin Healthcare System, Inc.;914 S 8
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<small>CITY, STATE, ZIP CODE, COUNTRY</small> Minneapolis, MN 55404-1204	<small>TYPE ESTABLISHMENT INSPECTED</small> Institutional Review Board
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(b) (4)	(b) (4)	(b) (4)	2/17/2018	2/17-18/2018	(b) (6)	2/19/2018
(b) (4)	(b) (4)	(b) (4)	7/12/2018	7/12/2018	(b) (6)	7/12/2018

B. IRB study # (b) (4) “ (b) (4) ” using a new unapproved non-invasive (b) (4), presented by the sponsor and clinical investigator as nonsignificant risk (NSR), and requesting waiver of signed consent, approved via expedited review 11/18/2016.

OBSERVATION 4

The IRB has no written procedure for conducting its initial and continuing review of research.

Specifically, there are no written procedures governing:

- A. Determination of additional safeguards for the IRBs Vulnerable Subjects category "impaired ability to give informed consent".
- B. Creation, maintenance, or use of the database utilized for tracking all studies and activities of the IRB.

***DATES OF INSPECTION**

8/07/2018(Tue), 8/08/2018(Wed), 8/10/2018(Fri), 8/15/2018(Wed), 8/16/2018(Thu), 8/21/2018(Tue), 8/22/2018(Wed), 8/23/2018(Thu)

Kellie L. Thommes
 Investigator
 X Signed By: Kellie L. Thommes -S
 Date Signed: 08-23-2018 10:48:18

SEE REVERSE OF THIS PAGE	<small>EMPLOYEE(S) SIGNATURE</small> Sharon L Matson, Investigator Kellie L Thommes, Investigator	<small>DATE ISSUED</small> 8/23/2018
	Sharon L Matson Investigator Signed By: Sharon L. Matson -S Date Signed: 08-23-2018 10:48:44 X	

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."