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July 30, 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: Prospective clinical trials comparing the safety and effectiveness of ketamine with those of other drugs for management of agitation

Dear Drs. Gottlieb and Menikoff:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, is writing in follow-up to our July 25, 2018, letter[1] 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.

Our July 25 letter explained how these clinical trials — which were conducted by investigators at the Hennepin County Medical Center 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 investigators and the Hennepin County Medical Center'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

[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 July 30, 2018.

experiments clearly involved research-stipulated interventions that far exceeded the minimal risk threshold.

We now wish to bring to your attention the July 26, 2018, report, *MPD Involvement in Pre-Hospital Sedation*, which was issued by the Office of Police Conduct Review (OPCR) in Minneapolis.[2] The report examines Minneapolis Police Department officers' involvement in Hennepin County Emergency Medical Services professionals' use of ketamine to sedate police detainees who were agitated. It appears that some of these detainees may have been enrolled in the second ketamine trial referenced in our July 25 letter.

A key piece of information, found at the top of page 4 of the OPCR report, is the following guideline for the use of ketamine found in Hennepin County Medical Center's current policy on behavioral emergencies involving adults:

> If the patient is **profoundly agitated** with active physical violence to himself/herself or others evident, and usual chemical or physical restraints (section C) may not be appropriate or safely used, **consider Ketamine** 5 mg/kg IM (If IV already established, may give 2 mg/kg IV/IO). [Emphasis added]

Importantly, the two ketamine trials described in our letter involved human subjects who ***were not profoundly agitated***, which the investigators themselves defined in their own writings[3,4] as +4 on the Altered Mental Status Scale (AMSS), an apparent research tool that was used routinely in agitation research at Hennepin County Medical Center. The above policy for ketamine use in profoundly agitated patients further confirms that the use of ketamine in subjects with less severe levels of agitation (AMSS scores of +2 or +3) in the two ketamine trials described in our July 25 letter was ***not*** consistent with usual care and represented a research intervention that exposed the subjects to risks that far exceeded minimal risk.

We hope this additional information convinces you — if you were not already convinced — of the urgent need for the FDA and OHRP to immediately launch formal compliance oversight investigations into the conduct and oversight of the two prospective clinical trials that tested ketamine and into the Hennepin County Medical Center's human subjects protection program. Public Citizen, the 64 cosigners of our July 25 letter, the Hennepin County community, and the broader public eagerly await confirmation that such investigations by your agencies are underway.

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[2] Office of Police Conduct Review, Minneapolis. *MPD Involvement in Pre-Hospital Sedation*. July 26, 2018. https://lims.minneapolismn.gov/Download/File/1389/Office%20of%20Police%20Conduct%20Review%20(OPCR)%20Pre-Hosptial%20Sedation%20Study%20Final%20Report.pdf. Accessed July 30, 2018.

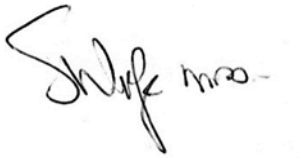
[3] Cole JB, Moore JC, Nystrom PC, et al. A prospective study of ketamine versus haloperidol for severe prehospital agitation. *Clin Toxicol (Phila)*. 2016;54(7):556-562.

[4] U.S. National Library of Medicine. ClinicalTrials.gov. Ketamine versus midazolam for prehospital agitation. Updated July 2, 2018. https://clinicaltrials.gov/ct2/show/NCT03554915. Accessed July 6, 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

cc: The Honorable Alex Azar, Secretary of Health and Human Services
Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA