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Citizen Petition

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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

On behalf of Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, and Public Citizen's Health Research Group, the undersigned submit this petition under Section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. § 355) and under Food and Drug Administration (FDA) regulations at 21 C.F.R. §§ 10.30, 56.121(b), and 312.70 to request the Commissioner of Food and Drugs to promptly take the following actions:

(1) Initiate clinical-investigator disqualification proceedings against Dr. Jon B. Cole, Dr. Lauren R. Klein, and their co-clinical investigators for repeatedly and deliberately initiating and conducting clinical investigations[1] of investigational drug products subject to section 505 of the FDCA without submitting or having in effect FDA-required investigational new drug applications (INDs) — violations that were detailed in warning letters issued to Dr. Cole and Dr. Klein on May 5 and May 6, 2021, respectively, and posted on the FDA's website on October 19, 2021.[2,3]

(2) Initiate disqualification proceedings against the institutional review board (IRB) (named the "Human Subjects Research Committee") at Hennepin County Medical Center/Hennepin Healthcare (HCMC) in Minneapolis, MN, for repeatedly failing to comply with the agency's regulations at 21 C.F.R. Part 50 (Protection of Human Subjects) and Part 56 (Institutional Review Boards) — noncompliance that adversely affected the rights and welfare of the vulnerable human subjects unwittingly enrolled in the clinical investigations conducted by Dr. Cole and Dr. Klein in violation of the FDA's IND requirements. This noncompliance was documented in the Form FDA 483,

[1] The terms "clinical investigation," "clinical trial," and "study" are used interchangeably throughout this petition.
[2] Food and Drug Administration. Warning letter to Jon B. Cole, M.D. May 5, 2021. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/jon-b-cole-md-611902-05052021. Accessed November 11, 2021.
[3] Food and Drug Administration. Warning letter to Lauren R. Klein, M.D., M.S. May 6, 2021. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/lauren-r-klein-md-ms-605544-05062021. Accessed November 11, 2021.

Inspectional Observations (483-Form) pursuant to the FDA's August 7-23, 2018, inspection of the HCMC IRB.[4]

(3) Require HCMC to develop and implement a plan for contacting the more than 1,700 human subjects (or the closest surviving family members of deceased subjects) who were unwittingly enrolled in the clinical investigations conducted by Dr. Cole and Dr. Klein without the subjects' legally effective informed consent and informing of them of (a) the serious regulatory violations documented by the FDA during its inspections of HCMC IRB and clinical investigator records related to those clinical investigations; and (b) the fact that the clinical investigators violated the subjects' rights and endangered the health and welfare of some subjects.

The pattern of repetitive egregious regulatory violations over the four-year period from July 2014 to July 2018 that were documented in the FDA's warning letters to Dr. Cole and Dr. Klein (and the related 483-Forms for the agency's 2019 inspections of their sponsor-investigator records) and in the 483-Form for the agency's 2018 inspection of the HCMC IRB demand the most serious compliance actions to hold these clinical investigators, the IRB, and HCMC appropriately accountable and to deter similar serious noncompliance by other clinical investigators and IRBs in the future. A slap-on-the-wrist approach for such noncompliance that significantly violated the rights of more than 1,700 vulnerable human subjects and endangered the health of safety of many of these subjects will not suffice.

Failure to take stronger compliance actions would send a signal to the research community and the public that the FDA is not serious about protecting the rights and welfare of human subjects, which would embolden other clinical investigators and IRBs to disregard the agency's IND and human subjects protection regulations.

A. ACTION REQUESTED

(1) Promptly initiate clinical-investigator disqualification proceedings against Dr. Jon B. Cole, Dr. Lauren R. Klein, and their co-clinical investigators for repeatedly and deliberately initiating and conducting clinical investigations of investigational drug products subject to section 505 of the FDCA without submitting or having in effect FDA-required INDs.

(2) Promptly initiate disqualification proceedings against the HCMC IRB for repeatedly failing to comply with the agency's regulations at 21 C.F.R. Parts 50 and 56.

(3) Promptly require HCMC to develop and implement a plan for contacting the more than 1,700 human subjects (or the closest surviving family members of deceased subjects) who were unwittingly enrolled in the clinical investigations conducted by Dr. Cole and Dr. Klein without the subjects' legally effective informed consent and informing of them

[4] Food and Drug Administration. Form FDA 483, Inspectional Observations for the inspection of the Human Subjects Research Committee/institutional review board at Hennepin County Medical Center/Hennepin Healthcare System, Inc. on August 7-23, 2018. https://www.citizen.org/wp-content/uploads/MIN-DO-Hennepin-Healthcare-System-INc.-Minneapolis-MN-FD-483-8-23-2018_LESS-Redacted.pdf. Accessed November 11, 2021.

of (a) the serious regulatory violations documented by the FDA during its inspections of HCMC IRB and clinical investigator records related to those clinical investigations; and (b) the fact that the clinical investigators violated the subjects' rights and endangered the health and welfare of some subjects.

B. STATEMENT OF GROUNDS

1. Regulatory background

FDA regulations at 21 C.F.R. § 312.70 stipulate that a clinical investigator (including a sponsor-investigator) may be disqualified if the investigator, among other things, has *repeatedly or deliberately* failed to comply with the requirements for investigational new drug applications under 21 C.F.R. Part 312 or with the requirements of 21 C.F.R. Part 50 (Protection of Human Subjects) or Part 56 (Institutional Review Boards).

Likewise, FDA regulations at 21 C.F.R. § 56.121(b) stipulate that an IRB may be disqualified if the Commissioner determines that (1) the IRB has refused or *repeatedly failed* to comply with any of the regulations set forth in 21 C.F.R. Part 56 and (2) the noncompliance adversely affected the rights or welfare of the human subjects in a clinical investigation. Importantly, FDA regulations at 21 C.F.R. §§ 56.111(a)(4) and (5) require that in order to approve research covered by 21 C.F.R. Part 56, the IRB must determine that informed consent will be sought and appropriately documented for each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by FDA regulations at 21 C.F.R. Part 50. Thus, an IRB's failure to ensure that the informed consent requirements of 21 C.F.R. Part 50 are implemented represents its de facto noncompliance with 21 C.F.R. Part 56.

2. Complaint letter about the clinical investigations testing the anesthetic ketamine versus potent sedatives (haloperidol or midazolam) for agitation in the prehospital setting

In a letter dated July 25, 2018, Public Citizen and 62 other individuals with expertise spanning, among other things, bioethics, medicine, human subjects protections, human rights, and law urged the FDA and the Department of Health and Human Services' (HHS') Office for Human Research Protections to immediately launch formal compliance oversight investigations into the conduct and oversight of two prospective clinical trials that involved comparing the safety and effectiveness of the general anesthetic ketamine with those of a potent sedative drug — haloperidol in one trial and midazolam in the other — for management of prehospital agitation (the ketamine clinical trials) without the human subjects' consent.[5]

Our July 25, 2018, letter explained how these ketamine clinical trials — which were conducted by investigators at HCMC — failed to (a) materially comply with key requirements of FDA and 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 characterized by the

[5] 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 November 11, 2021.

investigators and the HCMC IRB as involving 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, and such a waiver provision was not included in the FDA's human subject protection regulations at the time the trials were reviewed and approved by the IRB.

3. FDA's inspection of the HCMC IRB

Presumably prompted by our July 25, 2018, complaint letter, the FDA conducted an inspection of the HCMC IRB on August 7-23, 2018. According to the 483-Form issued for that inspection,[6] the FDA inspectors reviewed IRB records for at least four clinical trials, including the following:

- IRB#14-3841; study title: "Ketamine vs. Haloperidol for Severe Agitation in the Prehospital Setting;" approval date: 7/10/2014; review type: "Expedited;" study status: Closed 7/1/2016
- IRB#17-4306; study title: "Ketamine versus Midazolam for Prehospital Agitation;" approval date: 5/11/2017; review type: "Expedited;" study status: Paused 6/25/2018
- IRB#17-4345; study title: "Prospective Observational Investigation of Olanzapine versus Haloperidol versus Ziprasidone versus Midazolam for the Treatment of Acute Undifferentiated Agitation in the Emergency Department;" approval date: 5/22/2017; review type: "Expedited;" study status: Closed 5/1/2018
- A fourth listed trial with the IRB# and title redacted but which we presume, based on the FDA's May 6, 2021, warning letter to Dr. Klein,[7] was the following: IRB#18-4521; title: "Prospective Observational Investigation of Olanzapine versus Midazolam for the Treatment of Acute Undifferentiated Agitation in the Emergency Department;" approval date: 5/29/2018; review type: "Expedited:" study status: Paused 7/16/2018

The observations described in the 483-Form for the HCMC IRB inspection confirmed our earlier contention that there were unacceptable regulatory and ethical lapses in the oversight and conduct of the two ketamine clinical trials referenced in our July 25 letter, as well as at least two other clinical trials reviewed and approved by the HCMC IRB. In particular, the FDA inspectors made the following observations about the four above-referenced clinical investigations:

(1) The HCMC 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

[6] Food and Drug Administration. Form FDA 483, Inspectional Observations for the inspection of the Human Subjects Research Committee/institutional review board at Hennepin County Medical Center/Hennepin Healthcare System, Inc. on August 7-23, 2018. https://www.citizen.org/wp-content/uploads/MIN-DO-Hennepin-Healthcare-System-INc.-Minneapolis-MN-FD-483-8-23-2018_LESS-Redacted.pdf. Accessed November 11, 2021.
[7] Food and Drug Administration. Warning letter to Lauren R. Klein, M.D., M.S. May 6, 2021. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/lauren-r-klein-md-ms-605544-05062021. Accessed November 11, 2021.

determining the informed-consent requirements of FDA regulations at 21 C.F.R. Part 50, and these studies did 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, as required by FDA regulations at 21 C.F.R. § 56.111(b). 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.

The 483-Form for the HCMC IRB inspection also revealed that these four high-risk clinical trials involving highly vulnerable subjects had been inappropriately reviewed and approved by the IRB under an expedited review procedure, which under FDA regulations at 21 C.F.R. § 56.110 is permitted only for certain categories of research that involve no more than minimal risk. 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. Such a hasty and limited review procedure likely contributed to the inadequate review of the four high-risk trials.

Thus, the observations cited in the 483-Form for the HCMC IRB inspection clearly establish that over the nearly four-year period from July 2014 to May 2018, the HCMC IRB repeatedly failed to comply with the agency's regulations at 21 C.F.R. Part 50 and Part 56. Moreover, as explained below in the discussion of the FDA warning letters sent to Dr. Cole and Dr. Klein, each case of noncompliance by the HCMC IRB adversely affected the rights and welfare of vulnerable human subjects unwittingly enrolled in the clinical investigations conducted by these clinical investigators in violation of the FDA's IND requirements.

4. The FDA's warning letter to Dr. Jon B. Cole

On April 10-26, 2019, the FDA conducted an inspection of Dr. Cole's sponsor-investigator records for two clinical investigations. Objectionable conditions observed during the inspection were described in the 483-Form presented to Dr. Cole at the conclusion of the inspection[8] and in the FDA's subsequent May 5, 2021, warning letter to him.[9] This warning letter referenced the following two clinical investigations as being reviewed during the inspection:

[8] Food and Drug Administration. Form FDA 483, Inspectional Observations for the inspection of Jon B. Cole, M.D., Sponsor-Investigator, at Hennepin County Medical Center/Hennepin Healthcare System, Inc. on April 10-26, 2019. https://www.citizen.org/wp-content/uploads/FDA-Inspection-Jon-Coles-Clinical-Trials_April-2019.pdf. Accessed November 11, 2021.

[9] Food and Drug Administration. Warning letter to Jon B. Cole, M.D. May 5, 2021. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/jon-b-cole-md-611902-05052021. Accessed November 11, 2021.

- Protocol HSR 14-3841, "Ketamine vs. Haloperidol (Haldol) for Severe Agitation in the Pre-hospital Setting," of the investigational drugs ketamine and haloperidol
- Protocol HSR 17-4306, "Ketamine vs. Midazolam (Versed) for Severe Agitation in the Pre-hospital Setting," of the investigational drugs ketamine and midazolam

Both trials correspond to the two ketamine clinical trials referenced in our July 25, 2018, complaint letter to the FDA[10] and to the trials designated as IRB#14-3841 and IRB#17-4306 in the 483-Form for the August 2018 inspection of the HCMC IRB.[11]

The warning letter to Dr. Cole stated that "it appears that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects."[12] The warning letter proceeded to emphasize the following serious violation applicable to the conduct of both trials:

> **Failure to submit INDs for the conduct of clinical investigations with investigational new drugs subject to 21 CFR 312.2(a) [21 CFR 312.20 and 312.40(a)].** [Emphasis in original]
>
> FDA regulations require a sponsor to submit, and to have in effect, an investigational new drug application (IND) before initiating a clinical investigation of a drug subject to 21 CFR 312.2(a) in human subjects, unless the clinical investigation qualifies for an exemption (see 21 CFR 312.20 and 312.40(a)). You failed to comply with these requirements. Specifically, you initiated and conducted the following clinical investigations of investigational drug products subject to section 505 of the Federal Food, Drug, and Cosmetic Act without submitting and having in effect an IND
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> • The clinical investigation of the investigational drugs ketamine and haloperidol, conducted under Protocol HSR 14-3841
> • The clinical investigation of the investigational drugs ketamine and midazolam, conducted under Protocol HSR 17-4306[13]

The warning letter further provided a detailed refutation of Dr. Cole's written response to the 483-Form for his sponsor-investigator inspection in which he argued that the investigational drugs administered in these clinical investigations were not research interventions and, in the alternative, that even if these trials were clinical investigations subject to FDA jurisdiction, they

[10] 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 November 11, 2021.
[11] Food and Drug Administration. Form FDA 483, Inspectional Observations for the inspection of the Human Subjects Research Committee/institutional review board at Hennepin County Medical Center/Hennepin Healthcare System, Inc. on August 7-23, 2018. https://www.citizen.org/wp-content/uploads/MIN-DO-Hennepin-Healthcare-System-INc.-Minneapolis-MN-FD-483-8-23-2018_LESS-Redacted.pdf. Accessed November 11, 2021.
[12] Food and Drug Administration. Warning letter to Jon B. Cole, M.D. May 5, 2021. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/jon-b-cole-md-611902-05052021. Accessed November 11, 2021.
[13] *Ibid.*

met the criteria at 21 C.F.R. § 312.2(b)(1) for exemption from the requirements of 21 C.F.R. Part 312.

Regarding Dr. Cole's first argument, the FDA stated the following, in part, in its warning letter:

> For purposes of 21 CFR part 312, a clinical investigation is defined as "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part [312], an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice" [21 CFR 312.3(b)].
>
> The clinical investigations conducted under Protocols HSR 14-3841 and HSR 17-4306 involved the administration of haloperidol and ketamine, and of ketamine and midazolam, respectively, to human subjects. **Based on the information collected on inspection, Protocols HSR 14-3841 and HSR 17-4306 were designed to study the safety and efficacy of these drug products for the treatment of severe agitation, and severe agitation and profound agitation, respectively, in the pre-hospital setting.**
>
> **The use of these drug products was not "in the course of medical practice."** FDA has long held that when an investigator limits his choices, his patients' choices, and the choices of the people working for him in the treatment of those patients, then he is conducting a clinical investigation. This is different from the practice of medicine, where the primary intent is to treat the individual patient.
>
> Both protocols pre-specified the drug intervention to be administered to agitated subjects requiring chemical sedation during specified time periods. This was reinforced by removal of alternative treatment options from ambulances by your co-investigator, Dr. Jeffrey Ho, in his capacity as the Chief Medical Director for the Hennepin EMS [Emergency Medical System], and by consistent communication from Dr. Ho and from you, the sponsor-investigator, to EMT-Ps [Emergency Medical Technician-Paramedics] regarding the specific drugs and dosages that were to be administered during particular time periods. **As such, the clinical investigations limited the EMT-Ps' clinical judgment and limited the drug interventions that were available to the EMT-Ps for administration to each subject…**
>
> Consequently, the investigations conducted under Protocols HSR 14-3841 and HSR 17-4306 were clinical investigations of the investigational drugs ketamine and haloperidol, and of the investigational drugs ketamine and midazolam, respectively. **Under 21 CFR 312.20 and 312.40, you were required to submit and to have in effect INDs before initiating these clinical investigations.**
>
> Your statements that the drugs studied in Protocol HSR 14-3841 and Protocol HSR 17-4306 were not investigational drugs are not persuasive because they are inconsistent with the design and conduct of the clinical investigations. **The**

> **clinical investigations involved the prospective administration of specific drug products depending on the date of administration, the assessment and documentation of time to sedation, and the comparison of times to sedation among different drugs where the investigational drug was the independent variable of primary interest. Contrary to your assertions, both clinical trials required the EMT-Ps to administer a specific investigational drug to agitated subjects who were to be sedated chemically**. Whether a severely agitated subject in need of sedation received either ketamine or haloperidol while Protocol HSR 14-3841 was ongoing, or whether a severely or profoundly agitated subject in need of sedation received either ketamine or midazolam while Protocol 17-4306 was ongoing, **depended not on the clinical judgment of the EMT-Ps but on the date the EMT-Ps encountered the subject**... Finally, the fact that the drugs individually can be part of standard of care does not render them non-interventions in the study setting, as was the case here, where the protocols pre-specified the drug intervention that would be administered to agitated subjects requiring chemical sedation and limited both the EMT-Ps' clinical judgment and the interventions that were available to EMT-Ps for administration to each subject.[14]
>
> [Emphasis added]

Regarding Dr. Cole's second argument, in the alternative, that his clinical investigations met the criteria at 21 C.F.R. § 312.2(b)(1) for exemption from the requirements of 21 C.F.R. Part 312, the FDA responded with the following, in part:

> Your use of the investigational drugs (ketamine, haloperidol, and midazolam) in the clinical investigations conducted under Protocols HSR 14-3841 and HSR 17-4306 did not qualify for the exemption at 21 CFR 312.2(b)(1). **For example, these investigations did not satisfy the third exemption criterion above, found at 21 CFR 312.2(b)(1)(iii). That is to say, the investigations significantly increased the risks (or decreased the acceptability of the risks) associated with the use of the drug products.**
>
> Here, the clinical investigations conducted under Protocols HSR 14-3841 and HSR 17-4306 involved factors that significantly increased the risks (or decreased the acceptability of the risks) associated with the use of the drug products. First, Protocols HSR 14-3841 and HSR 17-4306 lacked an acceptable method for excluding pregnant women and pediatric patients, thus significantly increasing the risk with respect to those vulnerable study populations. Also, neither Protocol HSR 14-3841 nor Protocol HSR 17-4306 excluded subjects who were under the influence of intoxicants, in whom the use of ketamine is cautioned, nor did they provide precautions to better ensure the safety of these subjects. In addition, your protocols lacked specific measures to sufficiently guarantee the safety of study

[14] *Ibid.*

> participants in the pre-hospital setting. Therefore, these clinical investigations failed to meet the exemption criteria under 21 CFR 312.2(b)(1)(iii).[15]
>
> [Emphasis added]

Particularly disturbing were the following revelations in the FDA's warning letter to Dr. Cole:

> **We note that on May 15, 2014, you submitted IND 122826 for the investigational drugs ketamine and haloperidol in order to conduct a clinical trial that would have been substantially similar to the trial you sponsored and conducted under Protocol HSR 14-3841. You withdrew this IND following a June 10, 2014, teleconference with the Division of Psychiatry Products (DPP), during which DPP conveyed deficiencies with respect to your IND. These deficiencies were also shared with you in writing following the teleconference.** Among other things, DPP informed you that excluding "obviously gravid women" was not an acceptable or the standard method of exclusion of pregnant women in a trial. DPP also informed you that excluding subjects who "appear to be less than 18 years old" was not a reliable method to exclude pediatric patients, and that your protocol should include a reliable method to guarantee the exclusion of pediatric patients. In addition, DPP noted that ketamine labeling provides that caution should be used in the chronic alcoholic and the acutely alcohol-intoxicated patient, and that agitated patients in the pre-hospital setting run a high risk of being under the influence of various intoxicants. DPP recommended that you consider excluding from your study patients under the influence of various intoxicants. Finally, DPP noted ketamine labeling provides that ketamine should be used by or under the direction of physicians experienced in administering general anesthetics and in the maintenance of an airway and in the control of respiration, and that measures to guarantee the safety of study participants, including, for example, management of possible laryngospasm in a pre-hospital setting, should be clearly described in the protocol, given the ketamine safety profile.
>
> **Instead of addressing these deficiencies, you proceeded with a substantially similar clinical investigation of the investigational drugs ketamine and haloperidol under Protocol HSR 14-3841, and a follow-up trial of investigational drugs ketamine and midazolam under Protocol HSR 17-4306, without submitting or having in effect an IND. Moreover, neither Protocol HSR 14-3841 nor HSR 17-4306 addressed the concerns that DPP communicated to you.** The studies conducted under Protocols HSR 14-3841 and HSR 17-4306 significantly increased the risks and/or decreased the acceptability of the risks to subjects associated with the use of the investigational drug products in several ways that DPP had specifically identified.

[15] *Ibid.*

First, both protocols excluded "obviously gravid women, persons known to be less than 18 years old, and persons who obviously appear to be less than 18 years old." As DPP informed you, these are not acceptable, standard, or reliable methods for excluding pregnant women and children from clinical investigations. As a result, one pregnant woman was enrolled in Protocol HSR 14-3841, and two children under the age of 18 were enrolled in Protocol HSR 17-4306. **Administration of the investigational drugs to these subjects placed them at significantly increased risk of the adverse events associated with the investigational products and decreased the acceptability of those risks.**

Second, in both protocols you specifically noted that agitated patients who require sedation in the EMS setting "are frequently under the influence of drugs and/or ethanol." Despite these acknowledgments, the precaution included in the ketamine labeling, and DPP's concerns, **you did not exclude subjects under the influence of intoxicants from either study, nor did you include any precautions for subjects under the influence of such intoxicants in your protocols.** According to the published results for Protocol HSR 14-3841, the presenting Emergency Department median breath alcohol levels were 120 mg/dL in the ketamine group (n=23) and 160 mg/dL in the haloperidol group (n=70). Median serum alcohol levels were 220 mg/dL in the ketamine group (n=27). According to the published results of a urine drug screen performed on 37 of the 146 subjects enrolled in Protocol HSR 14-3841, four subjects tested positive for benzodiazepines and four subjects tested positive for opioids, specifically fentanyl, hydrocodone, and oxycodone. According to the published interim analysis of Protocol HSR 17-4306, the etiology of agitation was alcohol in 203 study subjects then enrolled (69%), with a median alcohol concentration of 220 mg/dL. The etiology of agitation was suspected drug intoxication in 133 study subjects then enrolled (38%). **Your failure to exclude, and the lack of any precautions for, subjects under the influence of various intoxicants significantly increased the risks and/or decreased the acceptability of the risks associated with the investigational drugs.**

Third, despite DPP's cautioning that ketamine should be used by or under the direction of physicians experienced in the maintenance of an airway and in the control of respiration, and that measures to guarantee the safety of study participants, including the management of possible laryngospasm in the pre-hospital setting, should be clearly described in the protocol, **you conducted both studies in the pre-hospital setting and did not put in place any specific measures to protect study participants.** According to the published results of Protocol HSR 14-3841, the intubation rate was significantly higher in the ketamine group, with 39% of subjects (25 out of 64) who received ketamine being intubated vs. 4% of subjects (3 out of 82) who received haloperidol being intubated. According to the published interim results of Protocol HSR 17-4306, 31% of subjects (20 out of 65) receiving ketamine 5 mg/kg were intubated, and 22% of subjects (31 out of 138) receiving ketamine 3 mg/kg were intubated. **The failure to take any specific safety precautions for the administration of**

> **ketamine in the pre-hospital setting when conducting clinical investigations significantly increased the risks associated with the use of this product.** [16]
>
> [Emphasis added]

The 483-Form presented to Dr. Cole also observed that, among other things, human subjects were enrolled in the ketamine trials without the clinical investigators obtaining the legally effective informed consent of the subjects (or from their legally authorized representatives) and that neither trial appeared 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.[17] (We also note that even if the ketamine trials had met the requirements for these exceptions from FDA informed consent requirements, the requirements for these exceptions were not satisfied by the clinical investigators or the HCMC IRB.) These findings represented appalling violations of the subjects' autonomy and FDA human subjects protection regulations.

5. The FDA's warning letter to Dr. Lauren R. Klein

On April 9-23, 2019, the FDA conducted an inspection of Dr. Klein's sponsor-investigator records for two clinical investigations. Objectionable conditions observed during the inspection were described in the 483-Form presented to Dr. Klein at the conclusion of the inspection[18] and in the FDA's subsequent May 6, 2021, warning letter to her.[19] This warning letter referenced the following two clinical investigations as being reviewed during the inspection:

- Protocol HSR 17-4345, "Prospective Observational Investigation of Olanzapine versus Haloperidol versus Ziprasidone versus Midazolam for the Treatment of Acute Undifferentiated Agitation in the Emergency Department," of the investigational drugs olanzapine, haloperidol, ziprasidone, and midazolam
- Protocol HSR 18-4521, "Prospective Observational Investigation of Olanzapine versus Midazolam for the Treatment of Acute Undifferentiated Agitation in the Emergency Department," of the investigational drugs olanzapine and midazolam

The first clinical trial corresponds to the one designated as IRB#17-4345 in the 483-Form for the August 2018 inspection of the HCMC IRB, and we presume that the second trial corresponds to

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[16] *Ibid*.

[17] Food and Drug Administration. Form FDA 483, Inspectional Observations for the inspection of Jon B. Cole, M.D., Sponsor-Investigator, at Hennepin County Medical Center/Hennepin Healthcare System, Inc. on April 10-26, 2019. https://www.citizen.org/wp-content/uploads/FDA-Inspection-Jon-Coles-Clinical-Trials_April-2019.pdf. Accessed November 11, 2021.

[18] Food and Drug Administration. Form FDA 483, Inspectional Observations for the inspection of Lauren R. Klein, M.D., Sponsor-Investigator, at Hennepin County Medical Center/Hennepin Healthcare System, Inc. on April 9-23, 2019. https://www.citizen.org/wp-content/uploads/FDA-Inspection-Lauren-Kleins-Clinical-Trials_April-2019.pdf. Accessed November 11, 2021.

[19] Food and Drug Administration. Warning letter to Lauren R. Klein, M.D., M.S. May 6, 2021. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/lauren-r-klein-md-ms-605544-05062021. Accessed November 11, 2021.

the fourth study listed under "OBSERVATION 1" in the same 483-Form that had an approval date of 5/29/2018.

The warning letter to Dr. Klein stated that "it appears that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects."[20] The warning letter proceeded to emphasize the following serious violation applicable to the conduct of both trials:

> **Failure to submit INDs for the conduct of clinical investigations with investigational new drugs subject to 21 CFR 312.2(a) [21 CFR 312.20 and 312.40(a)].** [Emphasis in original]
>
> FDA regulations require a sponsor to submit, and to have in effect, an investigational new drug application (IND) before initiating a clinical investigation of a drug subject to 21 CFR 312.2(a) in human subjects, unless the clinical investigation qualifies for an exemption (see 21 CFR 312.20 and 312.40(a)). You failed to comply with these requirements. Specifically, you initiated and conducted the following clinical investigations of investigational drug products subject to section 505 of the Federal Food, Drug, and Cosmetic Act without submitting and having in effect an IND:
>
> • The clinical investigation of the investigational drugs olanzapine, haloperidol, ziprasidone, and midazolam, conducted under Protocol HSR 17-4345
>
> • The clinical investigation of the investigational drugs olanzapine and midazolam, conducted under Protocol HSR 18-4521[21]

The warning letter further provided a detailed rebuttal of Dr. Klein's written response to the 483-Form for her sponsor-investigator inspection in which, like Dr. Cole, she argued that the investigational drugs administered in these clinical investigations were not research interventions and, in the alternative, that even if these trials were clinical investigations subject to FDA jurisdiction, they met the criteria at 21 C.F.R. § 312.2(b)(1) for exemption from the requirements of 21 C.F.R. Part 312. The FDA soundly rejected Dr. Klein's arguments with detailed statements that were essentially identical to those used in the agency's warning letter to Dr. Cole.[22]

Astonishingly, the FDA warning letter to Dr. Klein, like the one to Dr. Cole, also included the troubling revelation that she too had submitted an IND to the FDA for a clinical investigation that was substantially similar to the clinical trials cited in her warning letter and conducted without INDs being in effect. In particular, the FDA stated the following:

> **We note that on February 16, 2017, you submitted IND 134378 for the investigational drugs olanzapine, haloperidol, ziprasidone, and midazolam in order to conduct a clinical trial that would have been substantially similar to**

[20] *Ibid.*
[21] *Ibid.*
[22] *Ibid.*

> **the trial you sponsored and conducted under Protocol HSR 17-4345. In a March 24, 2017, teleconference with you, the Division of Psychiatry Products (DPP) placed IND 134378 on Full Clinical Hold.** In addition, DPP issued you a letter dated April 7, 2017, that explained the basis for the hold and detailed recommendations to address the deficiencies with the IND. Among other things, **DPP's letter specifically recommended that subjects with organ (liver or kidney) dysfunction and subjects taking medications with a known interaction with the study drugs be excluded from the study, based on risks of subject safety due to the proposed investigational drugs.**
>
> **Instead of addressing these deficiencies, you proceeded with a substantially similar clinical investigation of the investigational drugs olanzapine, haloperidol, ziprasidone, and midazolam under Protocol HSR 17-4345, and a follow-up trial of investigational drugs olanzapine and midazolam under Protocol HSR 18-4521, without submitting or having in effect an IND. Moreover, neither Protocol HSR 17-4345 nor HSR 18-4521 addressed the concerns DPP had communicated to you regarding the exclusion of these subjects from the study populations, based on the known risks of the investigational drugs.**
>
> Because the administration of the investigational drugs (olanzapine, haloperidol, ziprasidone, and midazolam) in these clinical investigations significantly increased the risks and/or decreased the acceptability of the risks associated with the use of these drug products, the exemption criterion at 21 CFR 312.2(b)(1)(iii) was not met, and you were required to submit and have in effect INDs before initiating these clinical investigations.
>
> [Emphasis added]

The 483-Form presented to Dr. Klein also observed that, among other things, human subjects were enrolled in Protocols HSR 17-4345 and HSR 18-4521 without the clinical investigators obtaining the legally effective informed consent of the subjects (or from their legally authorized representatives) and that neither trial appeared 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.[23] (We also note that, like Dr. Cole's ketamine trials, even if Dr. Klein's trials had met the requirements for these exceptions from FDA informed-consent requirements, the requirements for these exceptions were not satisfied by the clinical investigators or the HCMC IRB.) These findings again represented unacceptable violations of the subjects' autonomy and FDA human subjects protection regulations.

[23] Food and Drug Administration. Form FDA 483, Inspectional Observations for the inspection of Lauren R. Klein, M.D., Sponsor-Investigator, at Hennepin County Medical Center/Hennepin Healthcare System, Inc. on April 9-23, 2019. https://www.citizen.org/wp-content/uploads/FDA-Inspection-Lauren-Kleins-Clinical-Trials_April-2019.pdf. Accessed November 11, 2021.

6. Summary and conclusions

Dr. Cole and Dr. Klein should be promptly disqualified as clinical investigators

The circumstances described in the FDA's warning letters to Dr. Cole and Dr. Klein (and the related 483-Forms for the agency's 2019 inspections of their sponsor-investigator records) provided unequivocal, convincing evidence that they repeatedly and deliberately failed to comply with the requirements for INDs under 21 C.F.R. Part 312 and with the informed-consent requirements of 21 C.F.R. Part 50.

That Dr. Cole and Dr. Klein were repetitive violators of these IND and informed-consent requirements is obvious. Each was the principal clinical investigator and sponsor of two clinical investigations that were designed to study the safety and efficacy of investigational new drug products for the treatment of certain degrees of agitation in the prehospital (Dr. Cole) or hospital emergency department (Dr. Klein) setting. All four trials were conducted during the four-year period from July 2014 to July 2018 without an IND being submitted to the FDA and being in effect during the conduct of the trials and without complying with the informed-consent requirements of 21 C.F.R. Part 50. Dr. Cole also was a co-clinical investigator on Protocol HSR 17-4345, "Prospective Observational Investigation of Olanzapine versus Haloperidol versus Ziprasidone versus Midazolam for the Treatment of Acute Undifferentiated Agitation in the Emergency Department." The paper presenting the results of this trial, which published in 2018 in the *Annals of Emergency Medicine*, listed Dr. Klein as the first author and Dr. Cole as the last author.[24] The paper also reported that Dr. Cole was one of five individuals who "conceived the study." Thus, Dr. Cole was involved in the design or conduct of at least three of the noncompliant clinical investigations cited in the aforementioned FDA warning letters.

That Dr. Cole's and Dr. Klein's noncompliance was deliberate is evidenced by the sequence of events detailed in the FDA warning letters to them. Each of them — Dr. Cole in May 2014 and Dr. Klein in February 2017 — had submitted to the FDA INDs for investigational drugs in order to conduct clinical trials that were substantially similar to trials of the same investigational drugs that they subsequently conducted. However, the submitted INDs had been subsequently withdrawn (in the case of Dr. Cole) or placed on full clinical hold (in the case of Dr. Klein) because of serious deficiencies in the INDs identified by reviewers in the FDA's Division of Psychiatry Products. These IND deficiencies involved a lack of adequate provisions for excluding various subgroups of patients from the proposed IND clinical trials for whom the investigational drugs would have posed unacceptable risks of harm. FDA staff also had provided to Dr. Cole and Dr. Klein specific recommendations for addressing these deficiencies. Shockingly, both Dr. Cole and Dr. Klein then proceeded to repeatedly conduct substantially similar clinical investigations of the same investigational drugs without submitting or having in effect an IND and without addressing the FDA-identified deficiencies that posed unacceptable risk to some subjects. As a result, the clinical investigations conducted by Dr. Cole and Dr. Klein significantly increased the risks and/or decreased the acceptability of the risks associated with the use of the studied investigational drug products. It is therefore reasonable to conclude that Dr. Cole and Dr. Klein deliberately sought to circumvent the FDA's requirements for INDs

[24] 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.

under 21 C.F.R. Part 312, as well as the informed consent requirements of 21 C.F.R. Part 50, which apply to all clinical trials conducted under INDs.

In their June 4, 2021, correspondence responding to the FDA's warning letters, both Dr. Cole[25] and Dr. Klein[26] asserted that they did not intend to be out of compliance with or violate the FDA's IND requirements and that they mistakenly thought the uses of the drugs in their clinical trials were not research-related interventions and INDs therefore were not needed. They also described remedial actions that they had taken or planned to take, including the following: training on regulatory requirements for clinical trials and human subjects protections; engaging research mentors for their subsequent studies; and limiting the scope of their subsequent research activities.

These explanations and remedial actions are clearly insufficient and do not mitigate the need for the FDA to initiate clinical-investigator disqualification proceedings against them. First, their claims that they did not understand that INDs were needed for their clinical trials are not credible given their prior submissions of INDs to the FDA for substantially similar clinical trials. Second, although the remedial actions described by Dr. Cole and Dr. Klein are necessary steps, the egregious nature of their repeated noncompliance with the FDA's IND and human subjects protection regulations — which resulted in their violating the rights of more than 1,700 vulnerable human subjects and endangering the health and safety of many of these subjects — demand the most serious enforcement action to hold them appropriately accountable and to deter similar serious noncompliance by other clinical investigators.

Thus, there is more than sufficient justification for the FDA to initiate clinical-investigator disqualification proceedings against Dr. Cole and Dr. Klein under FDA regulations at 21 C.F.R. § 312.70.

Other clinical investigators should be disqualified

Dr. Cole and Dr. Klein did not act alone in designing and conducting the clinical trials cited in the May 2021 FDA warning letters addressed to them. Multiple other HCMC staff participated in these trials, which appear to have been part of a coordinated research program evaluating numerous investigational drug products for management of agitated patients. The FDA should identify all other co-clinical investigators who designed or conducted these trials and ascertain whether they were aware of Dr. Cole's and Dr. Klein's INDs that were submitted to the FDA for substantially similar trials and the FDA-identified deficiencies in those INDs. The FDA should initiate clinical-investigator disqualification proceedings against any co-clinical investigators who were aware of these circumstances. Dr. Jeffrey Ho, the Chief Medical Director for the Hennepin EMS who was identified as a co-clinical investigator for the ketamine trials in the

[25] Hennepin Healthcare. Letter to Sherry G. Bous, Pharm.D., Food and Drug Administration. June 4, 2021. https://www.hennepinhealthcare.org/wp-content/uploads/2021/10/FDA-Warning-letter-and-Hennepin-Healthcare-response-letter-Prehospital-May-June-2021.pdf. Accessed November 11, 2021. See PDF pages 10-15.
[26] Hennepin Healthcare. Letter to Sherry G. Bous, Pharm.D., Food and Drug Administration. June 4, 2021. https://www.hennepinhealthcare.org/wp-content/uploads/2021/10/FDA-Warning-Letter-and-Hennepin-Healthcare-response-letter-Hospital-MayJune-2021.pdf. Accessed November 11, 2021. See PDF pages 9 to 12.

FDA's warning letter to Dr. Cole,[27] is one key individual whom the FDA should carefully scrutinize for possible disqualification.

The HCMC IRB should be promptly disqualified

A well-trained and properly functioning IRB would have recognized that each of the above-referenced clinical investigations conducted by Dr. Cole and/or Dr. Klein involved more than minimal risk, required review at a convened meeting of the IRB, were not eligible for a waiver of informed consent under HHS regulations at 45 C.F.R. § 46.116(d), and could not be conducted without an appropriate exception from the FDA's informed consent requirements and submission of an IND to the agency.

As previously noted, the observations cited in the 483-Form for the HCMC IRB inspection clearly established that over the nearly four-year period from July 2014 to May 2018, the HCMC IRB repeatedly failed to comply with the agency's regulations at 21 C.F.R. Part 50 and Part 56. Moreover, as explained in the above discussion of the FDA warning letters sent to Dr. Cole and Dr. Klein, each case of noncompliance by the HCMC IRB adversely affected the rights and welfare of vulnerable human subjects unwittingly enrolled in the clinical investigations conducted by these clinical investigators in violation of the FDA's IND requirements.

In their June 4, 2021, correspondence responding to the FDA's warning letters, Dr. Cole[28] and Dr. Klein[29] also described steps that HCMC has taken or planned to undertake to strengthen its clinical research program and create a culture of compliance, including the following, among other things: implementing standardized protocol template for all investigator-initiated clinical trials; requiring institutional prereview of all IRB submissions that involve investigator-initiated clinical trials to assess whether an IND or investigational device exemption is needed; instituting mandatory training for all new research staff; and establishing a Public Research Advisory Board to improve community outreach and engagement and a Community Advisory Board.

Again, although such remedial actions are necessary steps, the egregious nature of the HCMC IRB's repeated noncompliance with the FDA's human subjects protection regulations — which cleared the way for Dr. Cole and Dr. Klein to violate the rights of more than 1,700 vulnerable human subjects and to endanger the health and safety of many of these subjects — demands the most serious enforcement action to hold it appropriately accountable and to deter similar serious noncompliance by other IRBs.

Thus, there is more than sufficient justification for the FDA to initiate disqualification proceedings against the HCMC IRB under FDA regulations at 21 C.F.R. § 312.70.

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[27] Food and Drug Administration. Warning letter to Jon B. Cole, M.D. May 5, 2021. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/jon-b-cole-md-611902-05052021. Accessed November 11, 2021.

[28] Hennepin Healthcare. Letter to Sherry G. Bous, Pharm.D., Food and Drug Administration. June 4, 2021. https://www.hennepinhealthcare.org/wp-content/uploads/2021/10/FDA-Warning-letter-and-Hennepin-Healthcare-response-letter-Prehospital-May-June-2021.pdf. Accessed November 11, 2021. See PDF pages 10-15.

[29] Hennepin Healthcare. Letter to Sherry G. Bous, Pharm.D., Food and Drug Administration. June 4, 2021. https://www.hennepinhealthcare.org/wp-content/uploads/2021/10/FDA-Warning-Letter-and-Hennepin-Healthcare-response-letter-Hospital-MayJune-2021.pdf. Accessed November 11, 2021. See PDF pages 9 to 12.

Institutional failure

Finally, the inexcusable regulatory and ethical lapses in the oversight and conduct of the clinical investigation conducted by Dr. Cole and Dr. Klein were indicative of systemic breakdowns in the HCMC's human subjects protection program. These breakdowns extended from the clinical investigators to the IRB to senior institutional officials.

A slap-on-the-wrist approach for such noncompliance that significantly violated the rights of so many human subjects and endangered their health and safety will not suffice. Failure to take stronger compliance actions would send a signal to the human subjects who were unwittingly enrolled in Dr. Cole's and Dr. Klein's high-risk clinical trials, the research community, and the public that the FDA is not serious about protecting the rights and welfare of human subjects, which would embolden other clinical investigators and IRBs to disregard the agency's IND and human subjects protection regulations.

The human subjects must be informed

Finally, and perhaps most importantly, the more than 1,700 human subjects who were unwittingly enrolled in the clinical investigations conducted by Dr. Cole and Dr. Klein deserve to be informed of (a) the serious regulatory violations documented by the FDA during its inspections of HCMC IRB and clinical investigator records related to those clinical investigations; and (b) the fact that the clinical investigators violated the subjects' rights and endangered the health and welfare of some subjects. The FDA therefore must direct HCMC to develop and implement a plan for contacting these human subjects (or the closest surviving family members of deceased subjects) and informing them of this information.

C. ENVIRONMENTAL IMPACT STATEMENT

We claim categorical exclusion under 21 C.F.R. § 25.31(a) from the environmental assessment requirement. An assessment is not required because the requested action would not increase the use of the active moiety that is the subject of this petition.

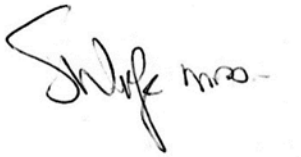
D. ECONOMIC IMPACT

Will be submitted upon request.

E. CERTIFICATION

We certify that, to the best of the knowledge and belief of the undersigned, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

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



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