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July 25, 2018

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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.
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Office for Human Research Protections
U.S. Department of Health and Human Services
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RE: Prospective clinical trials comparing the safety and effectiveness of ketamine with those of other drugs for management of agitation were conducted without the informed consent of the subjects, in violation of federal human subjects protection regulations

Dear Drs. Gottlieb and Menikoff:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, and the undersigned individuals — with expertise spanning, among other things, bioethics, medicine, human subjects protections, human rights, and law — are writing to request that the Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP) 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. Based on our review of available documents describing these clinical trials — which were conducted by investigators at the Hennepin County Medical Center in Minneapolis, MN — the trials 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, these 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 experiments clearly involved research-stipulated interventions that far exceeded the minimal risk threshold.

We note that both the FDA and OHRP have jurisdiction over these clinical trials. First, the trials were clinical investigations involving human subjects as defined by FDA human subjects protection regulations at 21 C.F.R. §§ 56.102(c) and (e). Second, the trials comprised research involving human subjects as defined by HHS human subjects protection regulations at 45 C.F.R. §§ 46.102(d) and (f), and the Hennepin County Medical Center holds an OHRP-approved Federalwide Assurance (FWA #6047) that applies to all non-exempt human subjects research regardless of sponsorship.[1]

The following is a detailed discussion of these trials and the serious regulatory and ethical lapses related to their oversight and conduct.

Overview of the clinical trials

Ketamine versus haloperidol trial for prehospital agitation

The first trial, a prospective clinical trial of ketamine versus haloperidol for purportedly severe prehospital agitation, was described by Cole et al in an article published in *Clinical Toxicology* in 2016.[2] The trial investigators enrolled adults age 18 or older who were managed by paramedics within the local emergency medical system (EMS) and had "severe acute undifferentiated agitation" prior to being transported to the Hennepin County Medical Center emergency department (ED).

For the purposes of the trial, agitation was scored using the Altered Mental Status Scale (AMSS), which appears to be a research tool that was "routinely used in agitation research" at Hennepin County Medical Center. The AMSS was an amalgam of previous scales[3] that had been developed to assess levels of alertness or sedation,[4] agitation,[5] or intoxication.[6] The AMSS score is a composite of ratings for the following four elements: responsiveness, speech, facial expressions, and eyes.

[1] Email communication with OHRP.
[2] 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.
[3] Martel M, Sterzinger A, Miner J, et al. Management of acute undifferentiated agitation in the emergency department: a randomized double-blind trial of droperidol, ziprasidone, and midazolam. *Acad Emerg Med*. 2005;12(12):1167–1172.
[4] Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the observer's assessment of alertness/sedation scale: study with intravenous midazolam. *J Clin Psychopharmacol*. 1990;10(4):244–251.
[5] Swift RH, Harrigan EP, Cappelleri JC, et al. Validation of the behavioral activity rating scale (BARS): a novel measure of activity in agitated patients. *J Psychiatr Res*. 2002; 36(2):87–95.
[6] Miner JR, Biros M. A standardized intoxication scale vs breath ethanol level as a predictor of observation time in the emergency department [abstract]. *Acad Emerg Med*. 2003; 10(5):520.

For the purposes of the trial, "severe agitation" was defined as an AMSS score of +2 (Responsiveness-anxious, agitated; Speech-loud outbursts; Facial Expression-normal; and Eyes-normal) or +3 (Responsiveness-very anxious, agitated, mild physical element of violence; Speech-loud outbursts; Facial Expression-agitated; and Eyes-normal). The trial excluded any patient with "profound agitation," which was defined as an AMSS score of +4 (Responsiveness-combative, very violent, or out of control; Speech-loud outbursts; Facial Expression-agitated; and Eyes-normal), because the investigators' institution "deemed it unethical and unwise to withhold ketamine from the most profoundly agitated patients at any time for both patient and caregiver safety."

The investigators used a prospective, open-label, nonrandomized design in which each subject's clinical trial group assignment and selection of intervention with ketamine or haloperidol was determined by the time period in which the subjects were enrolled, not by the clinical judgment of the health care professionals caring for the subjects. Specifically, the research interventions were described by the investigators as follows:

> To minimize potential bias introduced by seasonal changes, data were collected throughout an entire calendar year. **For the first three months of the study (October 2014–January 2015), the standard EMS operating procedure (SOP) for severely agitated patients was to treat acute undifferentiated agitation with 10 mg of IM haloperidol. For the next 6 months, haloperidol was removed from all ambulances in the system and the SOP for severely agitated patients was changed to 5 mg/kg of IM ketamine (dose calculation made by EMT-paramedic estimated weight in the field). For the final 3 months of the study, the SOP was returned to haloperidol 10 mg IM and haloperidol was reinstated on the ambulances**. [Emphasis added]

Thus, the clinical trial protocol dictated whether a particular subject with prehospital agitation would receive ketamine or haloperidol and precluded use of any other medication. Moreover, it appears that the care of all patients with agitation in the EMS system was potentially altered by the clinical trial protocol.

The primary outcome was the time to adequate sedation. Measurement of this outcome was done by the paramedics. The investigators described the training of the paramedics for the clinical trial as follows:

> All paramedics were trained in the AMSS, **a validated score of agitation routinely used in agitation research at the study institution**. Training was completed both online and at in-person training sessions led **by the primary investigator**. All paramedics were required to pass a quiz containing example patients where a correct AMSS score must be assigned. Upon encountering a patient with severe agitation requiring chemical sedation, paramedics activated a stopwatch immediately after injection of the sedative. Patients were excluded if stopwatch activation did not occur. AMSS scores were recorded every 5 minutes, or until adequate sedation was reached. Adequate sedation was defined clinically by the treating paramedic; however during training it was emphasized that adequate treatment of agitation would be an AMSS score < +1. Paramedics were specifically instructed to stop the stopwatch prior to 5 minutes if the patient appeared to

> have reached adequate sedation. **Paramedics also recorded prospectively if a legally authorized representative was present at the scene to give consent.** [Emphasis added]

Remarkably, despite the above description of the research procedures, the investigators asserted that "[t]his was a Waiver of Consent (45 CFR 46.116) prospective observational study."

The investigators also noted the following:

> Though this study was approved by the institutional IRB as a Waiver of Consent study, given the particularly vulnerable nature of this patient population a community consultation was performed in accordance with federal guidelines for Exception From Informed Consent (21 CFR 50.24) research. Both the caregivers affected by this study as well as a select group of patients at a local homeless shelter's inpatient chemical dependency program were consulted.

Between October 2015 and September 2016, 146 unwitting subjects were reportedly enrolled in the trial, 64 (57 with an initial AMSS score of +3 and seven with an initial score of +2) in the ketamine group and 82 (60 with an initial AMSS score of +3 and 22 with an initial score of +2) in the haloperidol group. Notably, adverse events, which included hypersalivation, emergence reactions, vomiting, dystonia, laryngospasm, akathisia, and death (one in the haloperidol group), were much more frequent in ketamine group subjects than in haloperidol group subjects (49 percent versus 5 percent, respectively; $p < 0.0001$). The rate of intubation was also significantly higher in ketamine group subjects than in haloperidol group subjects (39 percent versus 4 percent, respectively; $p < 0.0001$).

Ketamine versus midazolam trial for prehospital agitation

Even though the results of the first clinical trial clearly demonstrated that ketamine is significantly more dangerous than haloperidol for managing prehospital agitation as defined by an AMSS score of +2 or +3, some of the same investigators at Hennepin County Medical Center subsequently initiated a prospective clinical trial comparing ketamine with midazolam for purportedly severe or profound prehospital agitation. Details of the trial are available at ClinicalTrials.gov (NCT03554915).[7]

The trial, which began on August 1, 2017, and was suspended last month, appears to be using a design that is nearly identical to the ketamine versus haloperidol trial. The trial investigators enrolled adults age 18 or older who were managed by paramedics within the local emergency medical EMS and had purportedly severe agitation (an AMSS score of +2 or +3) or profound agitation (an AMSS score of +4) prior to being transported to the Hennepin County Medical Center ED. They had planned to enroll approximately 420 subjects between August 2017 and August 2018.

[7] 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.

The investigators again used a prospective, open-label, nonrandomized design in which each subject's clinical trial group assignment and selection of intervention with ketamine or midazolam was determined by the time period in which the subjects were enrolled, not by the clinical judgment of the health care professionals caring for the subjects. Specifically, the research interventions were described by the investigators as follows:

> Active Comparator: Ketamine-based Protocol
>
> The first 6 month period of the study will employ a ketamine-based protocol for prehospital agitation. There will be a tiered dosing protocol based on degree of agitation… For profoundly agitated (physically violent) patients, intramuscular ketamine 5 mg/kg will be administered first line. For severely agitated patients, intramuscular ketamine 3 mg/kg will be administered first line.
>
> Active Comparator: Midazolam-based Protocol
>
> The second 6 month period of the study will employ a midazolam-based protocol for prehospital agitation. There will again be a tiered dosing protocol based on degree of agitation… For profoundly agitated patients, intramuscular midazolam 15 mg will be administered. For severely agitated patients, intramuscular midazolam 5 mg will be administered.

Similar to the first trial, the ketamine versus midazolam clinical trial protocol dictated whether a particular subject with prehospital agitation would receive ketamine or midazolam and precluded use of any other medication, such as haloperidol, which was demonstrated in the first trial to be safer than ketamine. Moreover, it appears that the clinical care of all patients with agitation in the EMS system was potentially altered by the clinical trial protocol.

The primary outcome of the trial is the time from injection of drug to adequate sedation, defined as a score of +1 or less on the AMSS. The AMSS score was to be "determined by the treating paramedic," who was to "**undergo training as a research associate** prior to commencement of the trial" [emphasis added]. Subjects were to be followed for the duration of agitation, an expected average of 2 hours. Secondary outcome measures included the number of subjects who were intubated and the number of subjects who experienced each of the following: hypersalivation, apnea, nausea and vomiting, laryngospasm, and the need for rescue sedation.

A "NOTIFCATION OF ENROLLMENT" form that was provided to subjects (or subjects' caregivers) after their involvement in the research (copy enclosed) stated the following:

> You are receiving this form because you or someone you care for was included in a research study examining patients with agitation. This research study is being done to find out if one of two drugs, ketamine or midazolam is better for treating agitation… The Hennepin EMS System is undergoing a standard protocol change from one drug to the other; to compare which drug may be better the study doctors are collecting data on patients before and after the protocol change… Previous studies from our hospital suggest both drugs have similar risks…

> **Because this study involves collection of data in a setting where usual care was conducted, you were not consented prior to enrollment. This is permitted under federal regulations for Waiver of Consent Research (45 CFR 46.116(d)).** [Emphasis added]

Hennepin County Medical Center suspended the clinical trial on June 25, 2018, after troubling details about the conduct of the study — including the failure to obtain informed consent from the subjects for this greater-than-minimal-risk research and the apparent use of ketamine in patients who may not have been severely agitated — were exposed by the *Star Tribune*.[8,9] Following the trial's suspension, the institution issued a question and answer document defending the trial that stated the following, in part:[10]

> This study was considered observational (i.e. only collecting data) and "low risk" by the Institutional Review Board (IRB) that oversees patient safety in research studies at our institution. This means our research was not intended to intervene in the routine care or treatment of patients or the decision-making process of our clinicians or EMS staff. Instead, the intent was to review the effects of those patients already receiving a sedative, like ketamine, to determine which sedative, if required in the field, would be the safest for our patients.
>
> **What is your response to community concern about having a waiver of consent?**
>
> The federal requirements from the IRB approval process for this study were completely followed – including the waiver of consent to review data. This met all the ethical standards under which we conduct research, and we take this very seriously.

Assessment of risk in these prospective ketamine clinical trials: Both experiments involved far greater than minimal risk

FDA regulations at 21 C.F.R. § 56.102(i) and HHS human regulations at 45 C.F.R. § 46.102(i) define minimal risk as follows:

> *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

[8] Mannix A. Patients sedated by ketamine were enrolled in Hennepin Healthcare study. *Star Tribune*. June 23, 2018. http://www.startribune.com/patients-sedated-by-ketamine-were-enrolled-in-hennepin-healthcare-study/486363071/. Accessed July 6, 2018.
[9] Mannix A. Ketamine study at Hennepin Healthcare suspended after criticism from politicians. *Star Tribune*. June 26, 2018. http://www.startribune.com/ketamine-study-at-hennepin-healthcare-suspended-after-criticism-from-politicians-minneapolis-police-sedate/486507021/. Accessed July 6, 2018.
[10] Hennepin County Medical Center. Frequently asked questions about the use of sedatives. https://hennepinmedical.files.wordpress.com/2018/06/faqs-2018-6-262.pdf. Accessed July 7, 2018.

Application of this definition is central to any decision to approve a waiver of informed consent for research. Under HHS regulations at 45 C.F.R. § 46.116(d), an IRB may waive the requirements for informed consent provided the IRB finds and documents, among other things, that the research involves no more than minimal risk to the subjects. Notably, when the ketamine versus haloperidol trial was conducted, the FDA regulations did not provide for a waiver of the informed consent requirements similar to the HHS waiver provisions at 45 C.F.R. § 46.116(d), so such a waiver was not permissible for any FDA-regulated clinical trial. Under guidance issued by the FDA in July 2017, just before the ketamine versus midazolam trial began, such a waiver is now permissible.[11]

However, whether the two trials involved no more than minimal risk is not in question: A prospective clinical trial in which human subjects were assigned by a research protocol to receive the general anesthetic ketamine or a different powerful sedative drug for agitation, rather than according to the clinical judgment of the health care professionals caring for the subjects, clearly exceeded minimal risk and therefore was **not** eligible for waiver of informed consent under HHS regulations at 45 C.F.R. § 46.116(d).

Reliance on the AMSS research tool to define "severe agitation" likely lowered the threshold for using ketamine or other potent sedatives compared with usual care

Importantly, for the purposes of these clinical trials the investigators utilized the AMSS, which appears to be a "validated" research tool that was "routinely used in agitation research" at Hennepin County Medical Center.[12] However, the AMSS apparently was not routinely used by paramedics within the Hennepin County EMS system at the time these clinical trials were conducted, given the need for the investigators to train paramedics in use of the tool for the purposes of both trials.

For both trials, the investigators arbitrarily defined "severe agitation" as an AMSS score of +2 or +3. This definition of "severe agitation" likely was overly broad and resulted in some patients — particularly those at the lower end of this AMSS score range — being labeled as severely agitated and subsequently receiving the general anesthetic agent ketamine (or another powerful sedative drug) that they otherwise might not have received as part of usual care outside of the clinical trials. We note that there may be little difference subjectively between someone who appears anxious and restless (a component of an AMSS score of +1, which presumably represents mild agitation) and someone who appears anxious and agitated (a component of an AMSS score of +2, the lower end of the protocol-defined severe agitation range). In addition, the AMSS scale as interpreted by the investigators for the purposes of these trials appears to exclude a category of "moderate agitation." Thus, a patient could have been anxious and mildly or moderately agitated, had an AMSS score of +2, and been enrolled in these trials.

[11] Food and Drug Administration. IRB waiver or alteration of informed consent for clinical investigations involving no more than minimal risk to human subjects; guidance for sponsors, investigators, and institutional review boards. July 2017. https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM566948.pdf. Accessed July 6, 2018.

[12] 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.

Therefore, use of the AMSS research tool itself likely altered the interventions and risks to which the subjects were exposed in comparison to the usual care that they might have received had they not been enrolled in these clinical trials.

Risks of ketamine

Ketamine hydrochloride injection (sold under the brand name Ketalar and in generic versions) is a nonbarbiturate general anesthetic formulated for intravenous or intramuscular injection.[13] According to its FDA-approved product labeling, the drug is approved by the FDA only for the following indications:

- As the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation
- For the induction of anesthesia prior to the administration of other general anesthetic agents
- To supplement low-potency agents, such as nitrous oxide

The drug is not FDA-approved for management of agitation. The labeling cautions that the drug should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.

The product labeling for ketamine describes the following potentially serious adverse effects and risks of the drug:

- *Psychological*: Emergence reactions, which have occurred in approximately 12 percent of patients. The psychological manifestations of these reactions vary in severity between pleasant dream-like states, vivid imagery, hallucinations, and emergence delirium. In some cases, these states have been accompanied by confusion, excitement, and irrational behavior, which a few patients recall as an unpleasant experience. The duration of these reactions ordinarily is no more than a few hours; in a few cases, however, recurrences have taken place up to 24 hours postoperatively.
- *Cardiovascular*: Blood pressure and pulse rate are frequently elevated following administration of ketamine alone. However, hypotension and bradycardia have been observed. Arrhythmias also have occurred.
- *Respiration*: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of ketamine. Laryngospasms and other forms of airway obstruction have occurred during ketamine anesthesia.
- *Eye*: Diplopia and nystagmus have been noted following ketamine administration. It also may cause a slight elevation in intraocular pressure measurement.
- *Neurological*: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures.

[13] Par Pharmaceutical. Drug label: ketamine hydrochloride injection (KETALAR). April 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/016812s043lbl.pdf. Accessed July 6, 2018.

- *Gastrointestinal*: Anorexia, nausea, and vomiting have been observed.
- *General*: Anaphylaxis has been observed.

The drug also is contraindicated in patients in whom a significant elevation of blood pressure would constitute a serious hazard and in those who have hypersensitivity to the drug. Importantly, in contrast to the preoperative assessment of patients who are to receive ketamine as anesthesia for surgery or other invasive procedures, use of the drug by paramedics for agitation in most cases likely precludes an adequate assessment of whether a significant elevation of blood pressure would constitute a serious hazard in a particular acutely agitated patient and is therefore contraindicated.

Approximately two years prior to the initiation of the ketamine versus haloperidol trial, many of the investigators for these clinical trials had published a paper in *Prehospital Emergency Care* in 2013 that presented two case reports of the use of prehospital ketamine for the management of excited delirium syndrome, the most profound type of agitation.[14] In that paper, they explicitly warned that ketamine should be reserved for patients with excited delirium syndrome and should not be used in patients with lesser degrees (i.e., severe or less) of agitation because of the drug's known toxicities:

> **We would caution against using ketamine sedation in situations that do not warrant the immediate need for interruption of the severe, life-threatening, metabolic acidosis/catecholamine surge crisis seen in late-stage [excited delirium syndrome].** Clinicians should always consider the risk–benefit ratio of a possible intervention. In 2012, Burnett et al. described a case report of laryngospasm as a complication of prehospital ketamine administration in an agitated person. Laryngospasm is a known potential side effect of ketamine and can cause airway compromise. Although that person was labeled as an [excited delirium syndrome] patient, the details of that case (near normal pulse rate of 101 beats/min in the field with a respiratory rate of 18 breaths/min, normothermia, normal CK level, and a negative toxicology screen) make it unlikely to be late-stage [excited delirium syndrome] with an immediate threat to life. **Late-stage [excited delirium syndrome], where subjects are wildly agitated and violently exertional, should have marked tachycardia, hyperventilation secondary to metabolic acidosis, and hyperthermia with CK derangement. We would advocate that ketamine not be the chemical solution for every unruly or belligerent subjects [sic], as this would lead to overuse with unnecessary risk.** [Emphasis added]

The investigators further reported in their 2013 paper that Hennepin County's "EMS system standing-order protocol **reserves** the use of ketamine for profound agitation involving imminent risk of injury to patient or provider" [emphasis added]. The Hennepin County EMS system's standing-order protocol at that time thus appears to have precluded the use of ketamine in patients who did not have profound agitation.

[14] Ho JD, Smith SW, Nystrom PC, et al. Successful management of excited delirium syndrome with prehospital ketamine: Two Case Examples. *Prehosp Emerg Care*. 2013;17(2):274-279.

Nevertheless, disregarding their own advice, these investigators soon designed and conducted the ketamine versus haloperidol trial involving subjects who did not have excited delirium syndrome and instead had far less severe levels of agitation. And not surprisingly, their 2013 comments were prescient: As previously noted, adverse events, including laryngospasm, and the rate of intubation were significantly higher in ketamine group subjects than haloperidol group subjects, thus demonstrating that ketamine is significantly more dangerous than haloperidol for patients who have levels of agitation in the prehospital setting that are less severe than excited delirium syndrome.

In conclusion, the risks of exposure to ketamine obviously constituted the most substantial reasonably foreseeable risks to the subjects of both clinical trials, and those risks far exceeded the threshold of minimal risk, as defined by FDA and HHS human subjects protection regulations.

Risks of haloperidol and midazolam

Although the exposure of the research subjects to ketamine presented the greatest reasonably foreseeable risks to the subjects, exposure to either haloperidol or midazolam also exposed subjects to reasonably foreseeable risks of the clinical trials that exceeded minimal risk because the research protocols for these trials dictated when exposure to these drugs would occur for certain subjects, precluded other treatments, and likely resulted in some subjects receiving one of these potent sedatives when they otherwise might not have if they had been managed according to usual care.

The FDA-approved product labeling for haloperidol injection (sold under the brand name Haldol and in generic versions) indicates that the drug is approved only for the treatment of schizophrenia and the control of the tics and vocal utterances of Tourette's disorder.[15] The drug's many known risks include QT prolongation, cardiac arrhythmias, sudden death, tardive dyskinesia, and neuroleptic malignant syndrome.

The FDA-approved product labeling for midazolam (sold in generic versions only) indicates that the drug is approved only for preoperative sedation/anxiolysis/amnesia; sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic, or endoscopic procedures; induction of general anesthesia before administration of other anesthetic agents; sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting.[16] The drug's many known risks include respiratory depression, airway obstruction, oxygen desaturation, apnea, respiratory arrest, cardiac arrest, permanent neurologic injury, and death.

[15] Janssen Pharmaceuticals Companies. Drug label: haloperidol injection (HALDOL). December 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/015923s092lbl.pdf. Accessed July 7, 2018.
[16] Akorn Drug label: midazolam hydrochloride injection. November 2017. https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=737361a0-8db1-4d3c-ba5e-44df3f49fa22&type=pdf&name=737361a0-8db1-4d3c-ba5e-44df3f49fa22. Accessed July 7, 2018.

Failure to satisfy the requirements for obtaining the informed consent of the subjects under FDA and HHS human subjects protection regulations

In summary, the two clinical trials were not eligible for a waiver of informed consent under HHS regulations at 45 C.F.R. § 46.116(d) or under the FDA's July 2017 guidance on waiver of informed consent for certain research involving no more than minimal risk because the research clearly involved reasonably foreseeable risks that far exceeded the threshold of minimal risk.[17] The shocking failure by the Hennepin County Medical Center's IRB to recognize that these prospective clinical trials would expose subjects to greater-than-minimal-risk research interventions resulted in inappropriate waivers of informed consent. The oversight and conduct of these clinical trials thus flagrantly violated the requirements for obtaining the legally effective informed consent of the subjects (or the subjects' legally authorized representatives) under FDA regulations at 21 C.F.R. §§ 50.20 and 50.25 and HHS regulations at 45 C.F.R. § 46.116, regulations that are founded on the Belmont Report's basic ethical principles of respect for persons.[18]

We acknowledge that the investigators and the IRB alternatively could have considered whether these clinical trials were eligible for the exception from informed consent requirements for emergency research under FDA regulations at 21 C.F.R. § 50.24. However, it is unlikely that all provisions of these regulations could have been reasonably satisfied for either trial as designed and conducted.

Other regulatory lapses

But the regulatory lapses regarding the conduct and oversight of this trial extend well beyond those related to the assessment of risk and the waiver of informed consent. By failing to recognize that these prospective clinical trials involved greater than minimal risk to the subjects, the Hennepin County Medical Center's IRB also could not possibly have appropriately determined that the research satisfied the following criteria, among others, required for approval of research under FDA regulations at 21 C.F.R. § 56.111 and HHS regulations at 45 C.F.R. § 46.111:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

[17] Food and Drug Administration. IRB waiver or alteration of informed consent for clinical investigations involving no more than minimal risk to human subjects; guidance for sponsors, investigators, and institutional review boards. July 2017. https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM566948.pdf. Accessed July 6, 2018.

[18] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Ethical principles and guidelines for the protection of human subjects of research. April 18, 1979. https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf. Accessed July 7, 2018.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

These regulatory requirements are founded on the Belmont Report's basic ethical principles of beneficence and justice.[19]

Finally, it seems likely that these trials required investigational new drug applications (INDs) under FDA regulations at 21 C.F.R. 21 Part 312. The FDA advised in guidance issued in 2013[20] that an IND is needed for a clinical investigation of a marketed drug unless *all* of the following criteria for an exemption under FDA regulations at 21 C.F.R. § 312.2(b) are met:

(1) The drug product is lawfully marketed in the United States.

(2) The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.

(3) In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.

(4) The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 C.F.R. § 312.2(b)(1)(iii)).

(5) The investigation is conducted in compliance with the requirements for review by an IRB (21 C.F.R. Part 56) and with the requirements for informed consent (21 C.F.R. Part 50).

(6) The investigation is conducted in compliance with the requirements of 21 C.F.R. § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

As already discussed, these trials did not meet criterion 5. Moreover, these clinical trials also did not meet criterion 4 because they involved patient populations that significantly increased the

[19] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Ethical principles and guidelines for the protection of human subjects of research. April 18, 1979. https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf. Accessed July 7, 2018.
[20] Food and Drug Administration. Guidance for clinical investigators, sponsors, and IRBs: Investigational new drug applications (INDs) — Determining whether human research studies can be conducted without an IND. September 2013. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm229175.pdf. Accessed July 7, 2018.

risk and decreased the acceptability of the risk associated with use of ketamine. Thus, an IND was required for these clinical trials.

Conclusions and requested actions

The unacceptable regulatory and ethical lapses in the oversight and conduct of these two prospective clinical trials that involved testing the safety and effectiveness of the general anesthetic ketamine compared with other potent sedative drugs for management of prehospital agitation reflect systemic breakdowns in the Hennepin County Medical Center's human subjects protection program. These breakdowns extend from the investigators to the IRB to senior institutional officials.

Evidence that these systemic breakdowns encompass senior institutional officials can be found in the awkward and troubling efforts of Hennepin County Medical Center's leadership to defend the conduct and oversight of these clinical trials. For example, in a June 27, 2018, email sent to all Hennepin Healthcare employees regarding the ketamine versus midazolam clinical trial after it was suspended, Hennepin Healthcare's Chief Executive Officer Dr. Jon L. Pryor, stated the following:[21]

> It is important that **you have the facts**, specifically about these issues [emphasis added]:
> …
> **Waiver of Consent** [emphasis in original]
>
> - There has been a lot in the press about doing a study without consent which is referred to as "waiver of consent." **The majority of Waivers of Consent "involve studies in which there are minimal risks to subjects" and this is the category of the Ketamine study under current scrutiny, since we were only reviewing data** [emphasis added]. To quality [sic] for waiver of consent with minimal risk we need to follow specific federally regulated ethical standards. We closely follow these standards and are currently doing nothing different at Hennepin Healthcare – we are just like hundreds of other academic medical centers in the U.S.

Likewise, in a public statement posted on the institution's website, the medical center characterized the ketamine versus midazolam clinical trial as being "observational (i.e. only collecting data)" and "low risk,"[22] representations that cannot be reconciled with the descriptions of the research protocol found in other publicly available documents. Also, in response to the question, "**Is ketamine use common and is it safe to use with agitated patients?**" the institution's public statement misleadingly stated that "Hennepin EMS has been using ketamine as the standard of care for patients safely since 2008." But as noted above, some of the investigators for these clinical trials themselves explained in 2013 that ketamine was *not* the

[21] Copy of email received in a personal communication.
[22] Hennepin County Medical Center. Frequently asked questions about the use of sedatives. https://hennepinmedical.files.wordpress.com/2018/06/faqs-2018-6-262.pdf. Accessed July 7, 2018.

standard of care and should *not* be used for managing the type of agitated patients with AMSS scores of +2 and +3 who were enrolled in these clinical trials.[23]

A critical question for the FDA and OHRP is how many other ongoing and prior clinical trials conducted by the Hennepin County Medical Center have or had similar serious regulatory and ethical lapses? To ensure the protection of human subjects enrolled in clinical trials conducted by this institution, it is imperative that the FDA and OHRP promptly learn the answer to this question.

We therefore urge 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. These investigations should include (1) a rigorous FDA inspection of the institution's IRB and other clinical trials conducted by the same group of investigators that conducted the two ketamine clinical trials and (2) a comprehensive for-cause site visit by OHRP compliance oversight staff that examines IRB records for a wide array of clinical trials and other human subjects research.

We hope you share our concern regarding these troubling matters, and we look forward to a favorable response to our urgent request for investigations of the oversight and conduct of these clinical trials.

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

Sincerely,

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[23] Ho JD, Smith SW, Nystrom PC, et al. Successful management of excited delirium syndrome with prehospital ketamine: Two Case Examples. *Prehosp Emerg Care*. 2013;17(2):274-279.

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Enclosure

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

HENNEPIN COUNTY MEDICAL
LEVEL 1 TRAUMA CENTE
Minneapolis, MN 5541

CONSENT FOR CLINICAL INVESTIGATION CONDUCTED WITH PATIENTS

D/T/Int

Addressograph Label

NOTIFICATION OF ENROLLMENT

Project Title: Ketamine versus Midazolam Prehospital Agitation

You are receiving this form because you or someone you care for was included in a research study examining patients with agitation. This research study is being done to find out if one of two drugs, ketamine or midazolam, is better for treating agitation. Agitation is a state of extreme emotional disturbance where patients can become physically aggressive or violent, endangering themselves and those who are caring for them. The Hennepin EMS System is undergoing a standard protocol change from one drug to the other; to compare which drug may be better the study doctors are collecting data on patients before and after the protocol change. Experts have recommended both drugs for agitation; previous studies from our hospital suggest both drugs have similar risk, but the two have never been compared in the same study at any hospital.

While you were being treated by the EMS personnel, trained research associates monitored your vital signs, such as your heart rate and blood pressure, and wrote down the medications and treatments you received. Data was collected from medical information and blood samples obtained as part of your regular care. In addition, the study doctors may check the medical record to examine what happened during the hospital stay. The study participation and information will be kept completely confidential.

There was no cost to you to participate in this study, and you will not be charged. You will not be paid for your participation. Because this study involves collection of data in a setting where usual care was conducted, you were not consented prior to enrollment. This is permitted under federal regulations for Waiver of Consent Research (45 CFR 46.116(d)).

Your participation in this study will be kept completely confidential. The collected information will be identified only by a number assigned when you entered the study. Participation is voluntary; if you do not want your data used it will be removed.

If you have any questions regarding your participation in this study, please contact Dr. Jon Cole at (612) 873-8791. If you want to talk to someone other than the study doctor, you can call the Office of Human Subjects Research at Hennepin County Medical Center at (612) 873-6882 or write to:

Dr. Craig Peine, MD
Chair, Human Subjects Research Committee
Minneapolis Medical Research Foundation
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HSR # 17-4306 (March 30, 2017)

CONSENT FOR CLINICAL INVESTIGATION