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MEMORANDUM

TO: Jon L. Pryor, MD
Chief Executive Officer
Hennepin Healthcare

FROM: Donald M. Lewis
Elizabeth M. Winchell

DATE: January 23, 2019

RE: Assessment of Hennepin Healthcare's Response
To Prehospital Sedation Concerns (Ketamine)

1. Introduction and Scope of Review

Hennepin Healthcare System, Inc. ("Hennepin Healthcare") retained Nilan Johnson Lewis PA to assess its multi-part response to concerns regarding the administration of Ketamine and other sedatives by Hennepin Healthcare Emergency Medical Services ("Hennepin Healthcare EMS") paramedics to clinically agitated patients experiencing behavioral emergencies.

In early July 2018, Hennepin Healthcare determined that an "outside review" was necessary to address issues raised by the Minneapolis Department of Civil Rights Office of Police Conduct Review ("OPCR") draft report and the resulting media coverage and community reaction. As described below, three separate subjects of work were identified: EMS paramedic performance in the incidents identified in the OPCR draft report; EMS protocols regarding in-field use of Ketamine and the applicable standard of medical care; and the Hennepin Healthcare Institutional Review Board ("IRB") process regarding waiver of consent in Hennepin Healthcare research studies on EMS use of Ketamine. An internal task force was convened to address the first subject, and independent experts outside Minnesota were retained to review the remaining two.

We were retained in mid-July 2018 to assist Hennepin Healthcare "in evaluating and summarizing the results of pending investigations and reviews of EMS's administration of ketamine to individuals in the custody of the Minneapolis Police Department." Accordingly, our role was not that of an investigator. Rather, our task was to interpret and evaluate the work of other reviewers in a fashion that could be readily understood by both Hennepin Healthcare leadership and its stakeholders. We also hoped that our contribution would facilitate actions taken by Hennepin Healthcare in response to the public concerns about EMS use of Ketamine.

We monitored the work of the independent reviewers while it was in progress; attended their debriefing sessions following their interviews of Hennepin Healthcare staff; and were given access to the information they were provided. We also reviewed relevant background materials regarding the use and study of Ketamine; the OPCR's findings; selected footage of Minneapolis

Police Department ("MPD") Body Worn Camera ("BWC") video recordings of incidents cited by OPCR; and coverage and other information from secondary sources regarding Hennepin Healthcare, its EMS, and its response to the public concerns, including proposed remedial measures. As necessary, we engaged Hennepin Healthcare and EMS leadership with questions or issues of concern. Of course, we studied the reports of the internal working group and the independent reviewers once they were completed.

In this Memorandum, after describing the factual context giving rise to local attention to EMS use of Ketamine, we summarize the work and findings of the internal study group and the two independent reviewers. In our judgment, these key components of Hennepin Healthcare's response to the Ketamine controversy have already yielded valuable recommendations for process improvement.

2. Factual Background

a. Hennepin Healthcare EMS and IRB

Hennepin Healthcare, a subsidiary corporation of Hennepin County, operates an integrated care system including Hennepin County Medical Center ("HCMC"), a nationally recognized Level I Adult Trauma Center, Level I Pediatric Trauma Center, and acute care hospital, and a clinic system with locations throughout Hennepin County. Of relevance to our assessment, Hennepin Healthcare also operates a research institute, Hennepin Healthcare Research Institute, and the Hennepin Healthcare EMS system.

The Hennepin Healthcare EMS system is one of five EMS systems operating in Hennepin County.[1] Advanced Life Support ("ALS") protocols, containing guidelines for a variety of emergency medical scenarios, are approved by the Hennepin County EMS Council for use by all five Hennepin County EMS systems. However, each system is clinically guided by a medical director who is authorized by state statute to direct standard operating procedures to be followed by the specific EMS system for which the medical director is responsible.

The Hennepin Healthcare Research Institute, established in 1952, supports the conduct of medical research at Hennepin Healthcare. The Hennepin Healthcare Research Institute has earned accreditation from the leading, independent organization that accredits institutions that conduct medical research involving human subjects—the Association for the Accreditation of Human Research Protection Programs. The Hennepin Healthcare IRB, referred to as the Human Subjects Research Committee, is part of the Hennepin Healthcare Research Institute. The Hennepin Healthcare IRB, comprised of hospital and community representatives, scientists and non-scientists, is responsible for overseeing medical research involving human subjects that is conducted at Hennepin Healthcare. No human subjects research may proceed at Hennepin Healthcare without undergoing IRB review and approval. Once a research study is approved, the Hennepin Healthcare IRB monitors its progress and any problems that research subjects may encounter.

[1] The other four EMS systems operating in Hennepin County include Allina Health EMS, Edina Fire, North Memorial Ambulance, and Ridgeview Ambulance.

b. Ketamine: EMS Use and Research

Pursuant to Hennepin County ALS Protocol 3410 (attached hereto as Appendix), Hennepin Healthcare EMS can treat patients experiencing severe agitation with sedative medications.[2] Sedatives used in the care of agitated patients include medications known by the brand names Haldol, Versed, and Ketalar. Ketalar/Ketamine, which became a point of focus in publicity surrounding the sedation concerns, is a dissociative anesthetic that has been available for prescription use in the United States since the 1970s.

Prehospital Ketamine use to treat severe agitation within Hennepin Healthcare EMS began in 2008 and has increased since. Experts, both within and external to Hennepin Healthcare, have identified what they believe are three primary reasons for this increase. First, Ketamine leads to a faster onset of sedation than other available medications. Second, Ketamine has less effect on respiration than other available medications. Third, Ketamine has an optimal duration of sedation, in that the sedative effect may resolve within a timeframe that allows for effective examination once the patient reaches the Emergency Department.

Several Hennepin Healthcare physician researchers have contributed to a significant body of clinical research evaluating the use of chemical sedation by Hennepin Healthcare EMS paramedics to treat severe agitation in people experiencing behavioral emergencies. The more quickly a severely agitated patient can be sedated, the more quickly paramedics can safely treat and transport the patient. That more rapid onset of sedation in cases of serious agitation may be life-saving. Thus, a question of keen interest to these researchers is which of several medications achieves sedation in the shortest amount of time, with the least amount of risk to patients and providers.

Research was first conducted to assess intubation rates associated with the use of Ketamine in a population of "profoundly" agitated patients (based on the definition of "profound agitation" set forth in Hennepin County ALS Protocol 3410).[3] In this study, a team of researchers conducted a retrospective evaluation of the records of all patients who received prehospital Ketamine for control of profound agitation and who were subsequently transported to HCMC between May 1, 2010 and August 31, 2013. The researchers concluded that the use of "prehospital ketamine is associated with a high rate of endotracheal intubation in profoundly agitated patients; however, ketamine dosing is not associated with intubation rate when adjusted for potential confounders." The researchers also concluded that it "is likely that factors not included in [their] analysis,

[2] Throughout this Memorandum, the term "severe agitation" is used to describe a level of clinical agitation that warrants medical intervention. Both "severe" agitation and "profound" agitation, as defined by the Hennepin County ALS Protocol regarding behavioral emergencies, fit within our more general use of the term "severe agitation" herein. Our intention in referring to "severe agitation" throughout this Memorandum is to underscore that the type of agitation under discussion is distinct from and significantly more intense than ordinary, non-clinical agitation. The Hennepin County ALS behavioral emergencies protocol has sometimes been referred to mistakenly in underlying documents as protocol 3420.

[3] Olives TD, Nystrom PC, Cole JB, Dodd KW, Ho JD. Intubation of profoundly agitated patients treated with prehospital ketamine. *Prehosp Disaster Med*. 2016;31(6):593-602.

including both provider comfort with post-ketamine patients and anticipated clinical course, play a role in the decision to intubate patients who receive prehospital ketamine."

Research was later conducted to compare time-to-sedation between the medications Ketamine and Haldol in a population of "severely" agitated patients (based on the definition of "profound agitation" set forth in Hennepin County ALS Protocol 3410).[4] In this study, the team of researchers prospectively evaluated time-to-sedation during two six-month periods (between October 2014 and September 2015), when either Ketamine or Haldol was the first-line therapy for severe agitation. The researchers concluded that Ketamine is superior to Haldol in terms of time to adequate sedation for severe prehospital acute undifferentiated agitation, but is associated with more complications and a higher intubation rate.

More recently, researchers initiated a study to compare time-to-sedation between the medications Ketamine and Versed in a population of "severely" and "profoundly" agitated patients.[5] The Ketamine/Versed study was proactively paused on June 25, 2018, after the sedation concerns drew public attention. Both studies faced criticism for utilizing "waiver of consent" – an option for designing studies that allows researchers to involve people in research who have not agreed in advance to participate, when stringent regulatory and ethical requirements are satisfied. In this case, "waiver of consent" was the only feasible way to conduct the sedation research prospectively because it is not possible to routinely obtain consent from severely agitated patients experiencing behavioral emergencies. While the ethical norms and federal regulations underlying "waiver of consent" research are complex, an important concept is that much "waiver of consent" research is only permitted to proceed when researchers and an IRB agree that the research presents no more than a minimal risk of harm to participants.

c. Minneapolis OPCR Study

The OPCR is an office of the Minneapolis Department of Civil Rights that investigates allegations of police misconduct. In the fall of 2017, during OPCR's first audit of MPD BWC, OPCR analysts observed multiple incidents during which EMS professionals injected sedatives into individuals detained by police officers. In some instances, the EMS administration of the sedative appeared to OPCR analysts to have been directed by the police officers. The OPCR analysts also questioned whether the detainees involved were "profoundly agitated" within the meaning of Hennepin County ALS Protocol 3410.

At the request of the Civil Rights director, OPCR conducted a study exploring the use of Ketamine during MPD calls for service. The study involved review of police reports that included references to Ketamine use, followed by retrieval and review of corresponding BWC videos. In its draft report dated May 24, 2018, OPCR staff found that "in many cases" the

[4] 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. *See also* 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.
[5] U.S. National Library of Medicine. ClinicalTrials.gov. Ketamine versus midazolam for prehospital agitation. Updated July 11, 2018. https://clinicaltrials.gov/ct2/show/NCT03554915. Last accessed January 21, 2018.

administration of Ketamine met the EMS protocols. However, OPCR observed "numerous cases that did not appear to meet the 'profound agitation' standard." The draft report noted that:

- Use of Ketamine on MPD detainees increased nearly tenfold between 2010 and 2017, from six to 62 incidents, and 11 incidents had already been reported in the first four months of 2018.

- MPD officers "explicitly asked EMS to provide ketamine" and assisted EMS personnel during administration of the sedative, often while the subject was restrained.

The OPCR draft report described at least six episodes of Ketamine use by EMS in the field, highlighting casual comments by MPD officers urging the injection of the sedative; verbal resistance by subjects to the injections; administration of the sedative while the subject did not appear agitated or was already restrained; and subjects who required intubation following ketamine injection.

While the study was in progress, the Civil Rights director notified MPD of OPCR's study and its initial concerns. In response, MPD issued an "administrative announcement" on May 18, 2018, stating that "MPD Officers shall never suggest or demand EMS Personnel 'sedated' a subject. This is a decision that needs to be clearly made by EMS Personnel not MPD Officers." The OPCR draft report also included recommendations for additional policies, training, and reporting by MPD officers regarding their interactions with EMS professionals regarding the use of sedatives in the field.

Hennepin Healthcare challenged the findings of the draft report, first in a May 30, 2018 memorandum from the EMS Medical Director. Following meetings with City representatives and OPCR staff, Hennepin Healthcare submitted an official written response on July 23, 2018. The response challenged numerous inaccuracies in the OPCR draft report, and underscored that (a) Ketamine was widely accepted within the medical community as a safe and fast-acting sedative; (b) decisions by EMS paramedics to administer Ketamine were driven by the professional judgment on medical necessity and not directed by law enforcement; (c) OPCR investigators were unqualified to make medical judgments on Ketamine use; and (d) OPCR mischaracterized the applicable EMS protocols.

OPCR's final report, dated July 26, 2018, noted that its authors were not medical professionals and were "not attempting to provide any opinion on medical courses of action" taken in the eight case studies detailed in the final report. Included among the report's appendices were the May 30 memorandum and July 23 written response. The final report's conclusions and recommendations focused on revisions to MPD policy; the only implication for HHS involved potential notice to the City and MPD regarding future medical research.

d. Media Reports and Public Citizen Letter

Media coverage involving the sedation concerns began with publication of the leaked draft OPCR report in the Star Tribune on June 14, 2018. A subsequent series of Star Tribune articles

included reporting on consumer advocacy group Public Citizen's open letter to the U.S. Food and Drug Administration ("FDA") and the U.S. Department of Health and Human Services Office for Human Research Protections ("OHRP"), and articles focusing on the perspective of people who had been sedated by Hennepin Healthcare EMS.

In its July 25, 2018 open letter, Public Citizen alleged that Hennepin Healthcare's prehospital sedation research failed to (a) materially comply with key requirements of FDA and OHRP regulations for the protection of human subjects, and (b) satisfy the basic ethical principles upon which those regulations are founded. The open letter further alleged that the Hennepin Healthcare IRB incorrectly determined that the research involved no more than minimal risk to participants, such that the IRB should not have approved waiver of informed consent. Public Citizen sought for-cause inspections of Hennepin Healthcare's research activities by the FDA and OHRP.

e. Pending Legal and Regulatory Reviews

Civil Litigation. We are aware of one civil lawsuit, commenced in Hennepin County District Court in November 2018, by a woman who was allegedly taken into custody in December 2017 during a welfare check in her Minneapolis apartment, handcuffed and restrained on a gurney in an ambulance, administered Ketamine over her objections, and intubated upon her arrival at HCMC. The complaint contains extensive allegations regarding Hennepin Healthcare's research studies involving EMS use of sedatives, and asserts that EMS "changed the protocol in a way that eliminated choice and mandated sedation with ketamine for all agitated patients despite their level of agitation." The core legal claims are use of excessive force and medical malpractice.

Regulatory Reviews. A variety of regulatory activities relating, at least in part, to the sedation concerns are presently underway. At the federal level, the FDA conducted an inspection of the Hennepin Healthcare IRB between August 7 and August 23, 2018 and is expected to issue its conclusions within the next several months. At the state level, Hennepin Healthcare requested on June 22, 2018 that the Minnesota Emergency Medical Services Regulatory Board ("EMSRB") conduct a formal review of the complaints regarding Ketamine use reported by the OPCR. EMSRB confirmed in June 2018 that it would conduct such a review, but it is unclear when EMSRB will issue a response regarding its findings.

f. Engagement of Reviewers

In July 2018, Hennepin Healthcare leadership commenced a review of the OPCR draft report, EMS practices and protocols related to the in-field use of Ketamine and other sedatives, and the processes leading to the IRB's review and approval of the two sedation studies. The objectives of the review, as stated in the Hennepin Healthcare leadership's memorandum to the Board's executive and governance committees, were to address the following questions:

- Was Hennepin Healthcare EMS inappropriately influenced by the Minneapolis police officers in the use of a sedative (as suggested by the draft OPCR report)?

- Did Hennepin Healthcare EMS follow Hennepin County EMS System Protocol and EMS standing orders on the use of sedatives in prehospital settings and does the current protocol meet the standard of medical care?

- Did Hennepin Healthcare's IRB process on waiver of consent in the sedative study follow regulations?

The organization of the outside review aligned with categories suggested by the above questions:

- *Review of the OPCR draft report.* A working group of Hennepin Healthcare physicians, administrators, and executive and legal staff—led by senior Hennepin Healthcare clinical leadership—would review the OPCR draft report and its underlying evidence—including police reports and BWC videos. Additionally, the EMSRB would conduct its own review of the episodes described in the OPCR draft report to determine if the use of sedatives met medical criteria.

- *Review of EMS clinical protocols and practice.* Hennepin Healthcare retained two outside experts—both from Dallas, Texas—to review EMS protocols for use of sedatives and whether those protocols were followed in the field. Raymond Fowler, M.D. (a professor and chief of the EMS division of the University of Southwest Texas Medical Center and former president of the National Association of EMS Physicians) and Brian Williams, M.D. (medical director of the Community Health Institute for the Parkland Health and Hospital System and current Chair of the Dallas Citizens Police Review Board).

- *Review of the IRB process and waiver of consent*. Heidi Gertner, J.D. and Sara Goldkind, M.D. M.A.—both from metropolitan Washington, DC—were retained to assess the IRB review and approval of the two sedation studies. Gertner (a partner with the Hogan Lovells law firm focusing on drug regulation) and Goldkind (an authority on clinical research ethics and principal with Goldkind Consulting) each has more than ten years' prior work experience with the FDA.

3. Summary of Review Findings

Below, we summarize the method and findings of (a) the review of the OPCR draft report, (b) the review of EMS clinical protocols and practice, and (c) the review of research activities, including IRB review and approval and decision making regarding waiver of consent.

a. Internal Working Group Review

In July 2018, a diverse, multi-disciplinary working group of Hennepin Healthcare physicians, administrators, and executive and legal staff (the "Working Group") reviewed the OPCR draft report and its underlying evidence—including police reports, EMS run sheets, and BWC videos depicting police incidents where Hennepin Healthcare EMS responded to medical emergencies.

A designated clinical moderator led the viewing of BWC videos; EMS and Emergency Medicine providers within the Working Group assessed the clinical judgment observed in the BWC videos. The Hennepin County Attorney's Office subsequently prepared a memorandum describing the Working Group's review and its findings.

The Working Group's key finding was that Hennepin Healthcare EMS acted independently with respect to the administration of Ketamine to every patient portrayed in the BWC videos, whether or not an MPD officer suggested using the medication.

Notably, the Working Group also documented findings that stand in stark contrast to the OPCR draft report. First, no incidents of cardiac arrest involving patients who received Ketamine were observed, despite contrary information in the OPCR draft report. Second, no incidents of prehospital endotracheal intubation involving patients who received Ketamine were observed, despite contrary information in the OPCR report. Third, only one reference to prehospital sedation research being conducted at Hennepin Healthcare was observed, despite the OPCR draft report's suggestion that the existence of such research may have affected Hennepin Healthcare EMS behavior.[6]

The Working Group also made important findings regarding areas for improvement. First, the Working Group identified that training to assist paramedics in understanding how best to interact with law enforcement would be valuable, with an emphasis on training paramedics to assert the necessary authority to ensure appropriate patient care is provided. Second, the Working Group expressed concern regarding a situation in which MPD officers appeared to threaten a patient with a potential medical intervention (i.e., the administration of Ketamine). The Working Group was unified in its position that medical interventions should never be threatened by police or used punitively. The Working Group again identified that it would be valuable to implement training to strengthen law enforcement/Hennepin Healthcare EMS collaboration during behavioral emergencies, while simultaneously clarifying roles and expectations for all those involved. Third, the Working Group noted that in a small number of the incidents reviewed, Hennepin Healthcare EMS failed to demonstrate the level of professionalism that is expected by Hennepin Healthcare and the public.

b. Clinical Review

Review of EMS clinical protocols and practice. Dr. Raymond Fowler and Dr. Brian Williams (the "Clinical Reviewers") conducted a focused review of Hennepin Healthcare EMS prehospital sedation practices. Their work included review of relevant policies, protocols, and guidelines, as well as clinical documentation reflecting the care of patients sedated by Hennepin Healthcare EMS. The Clinical Reviewers visited the Hennepin Healthcare campus on separate dates in August 2018.[7] While onsite, the Clinical Reviewers interviewed and engaged in constructive

[6] In this case, a Hennepin Healthcare EMS provider mentioned the research to an MPD officer following transportation of a patient who had received Ketamine to the Hennepin Healthcare Stabilization Room.

[7] Dr. Fowler visited Hennepin Healthcare on August 14, 2018, and Dr. Williams visited Hennepin Healthcare on August 31, 2018.

dialogue with stakeholders, including the Hennepin Healthcare EMS Medical Director, the Hennepin Healthcare EMS Chief and Assistant Chief, the Chief of Emergency Medicine at Hennepin Healthcare, members of Hennepin Healthcare IRB leadership, and certain Hennepin Healthcare physician researchers. In addition, the Clinical Reviewers each had the opportunity to review and ask questions regarding MPD BWC videos involving Hennepin Healthcare EMS, including videos referenced in the OPCR draft report. The Clinical Reviewers subsequently provided a written report that described their review and findings, and which responded to specific questions that had been posed by Hennepin Healthcare.

During interactive meetings with Hennepin Healthcare stakeholders, the Clinical Reviewers each opined that they supported the prehospital use of sedatives to treat severe agitation and viewed such treatment as consistent with a national standard of care. The Clinical Reviewers also opined that it appeared to them that prehospital use of sedatives to treat severe agitation by Hennepin Healthcare EMS was consistent with the applicable local standard of care. In their written report, the Clinical Reviewers also described their impression that Hennepin Healthcare EMS paramedics and others involved in the care of Hennepin Healthcare patients who are sedated in the prehospital setting receive extensive training.

The Clinical Reviewers' report also identified areas for improvement. First, the Clinical Reviewers opined that patients who are receiving Ketamine as a sedative for the treatment of agitation must be closely monitored by Hennepin Healthcare EMS paramedics in a robust way. Per the Clinical Reviewers, this would involve a paramedic physically located at the patient's side, use of an electrocardiogram ("ECG") monitor, availability of suction, taking frequent vital signs, continuous pulse oximetry, and waveform capnography. Hennepin County ALS Protocol 3410 guides paramedics to transport patients who have received Ketamine rapidly to the ambulance and to prepare to provide respiratory support and other monitoring, but does not expressly provide for each of the features of robust monitoring described by the Clinical Reviewers.

In addition, the Clinical Reviewers indicated that ongoing training, Continuous Quality Improvement ("CQI") activities, and retrospective case review are "essential" to the prehospital use of Ketamine. The Clinical Reviewers noted that they received input from stakeholders during their review as to the limited resources that have historically been available for Hennepin Healthcare EMS CQI.

The Clinical Reviewers did not offer a specific opinion on the question of whether patients who are sedated with Ketamine typically face more complications and/or poorer outcomes than patients who are sedated with other medications. Examples of possible complications and adverse outcomes include respiratory difficulties, including those necessitating intubation and/or ICU care; hallucinations and other acute psychiatric symptoms; and longer hospital stays. However, during interactive meetings with Hennepin Healthcare stakeholders, the Clinical Reviewers expressed positive views regarding the safety profile of Ketamine, including when used by EMS in the prehospital setting.

c. Research Review

Heidi Gertner, J.D. and Sara Goldkind, M.D., M.A. (the "Research Reviewers") conducted a focused audit of study design and IRB review and approval activities pertaining to the Ketamine/Haldol and Ketamine/Versed studies, as well as ten additional waiver of consent studies that were proactively paused in Summer 2018. Their work included both an onsite compliance review and an offsite documentation review. While visiting the Hennepin Healthcare campus between August 7 and August 9, 2018, they jointly reviewed selected Hennepin Healthcare IRB files, Hennepin Healthcare IRB policies, protocols for studies reviewed by the Hennepin Healthcare IRB, and regulatory correspondence. The Research Reviewers also conducted interviews with numerous stakeholders, including, but not limited to, the former and current Chairs of the Hennepin Healthcare IRB, the Hennepin Healthcare EMS Medical Director, Hennepin Healthcare physician researchers, and the Hennepin Healthcare EMS Chief and Assistant Chief. Following the onsite compliance audit, the Research Reviewers audited the ten additional paused waiver of consent studies. Upon completing both the onsite and offsite portions of their audit, the Research Reviewers provided a written report that described their review and findings, offered suggestions for improvement, and responded to specific questions that had been posed by Hennepin Healthcare.

The Research Reviewers' audit was designed to assess compliance with regulatory requirements for research involving human participants, including the U.S. Department of Health and Human Services "Common Rule" regulations set forth at 45 Code of Federal Regulations ("CFR") Part 46 and FDA regulations set forth at 21 CFR Parts 50 and 56. Importantly, while the Research Reviewers identified instances of technical regulatory noncompliance, they opined that, with respect to the two studies involving Ketamine: (1) individuals enrolled in these studies were not exposed to any additional risk as a result of participating in the research, when compared with risks they would have faced had they not participated in the research, (2) no serious or continuing noncompliance occurred in these studies, and (3) none of the mistakes or technical noncompliance identified caused unexpected serious harm to patients, so as to require suspension or termination of the research under FDA regulations.

Notably, the Research Reviewers are familiar with Public Citizen and had an opportunity to review and consider the positions expressed in the Public Citizen letter. Of particular emphasis, the Research Reviewers did not feel the use of a cluster-randomized study design based on changes to the behavioral emergencies protocol followed by Hennepin Healthcare EMS was problematic under applicable regulations or ethical norms. In reaching this conclusion, the Research Reviewers considered that the Hennepin Healthcare EMS Medical Director is duly authorized by state statute to set medication administration protocols for the system he oversees, including when doing so results in a deviation from a higher-level, applicable system protocol, such as the Hennepin County ALS Protocols. Although the Public Citizen letter argued that changing the protocol in this way inappropriately affected the treatment of all Hennepin Healthcare EMS patients (not just those who would ultimately participate in the research), the Public Citizen letter ignored that the Hennepin Healthcare EMS system, through its Medical Director, is authorized to set, modify, and discontinue standard operating procedures to improve patient care.

4. Assessment and Recommendations

In our assessment, Hennepin Healthcare's multi-part review validates important aspects of its EMS and research operations, while also uncovering critical areas for accountability and improvement. For example:

- Possessing an expert level of knowledge regarding the benefits and risks of prehospital Ketamine use, the Clinical Reviewers conclude that its use is sound, within the standard of care, and consistent with clinical best practices for the prevention of severe metabolic acidosis. The Clinical Reviewers also discern a critical need for an organized, systematic approach to quality assessment and performance improvement within Hennepin Healthcare EMS.

- The Working Group determined that Hennepin Healthcare EMS paramedics demonstrated independent and appropriate clinical decision making in each Hennepin Healthcare EMS encounter referenced in the OPCR draft report. However, the Working Group also reached consensus on the need for training to support paramedic command of patient care on a scene shared with MPD or other law enforcement.

- The Research Reviewers opine that mistakes involving study descriptions and IRB processes did not increase the risks of research participation, nor did they cause any participant to be exposed to more than a minimal risk of harm. Of emphasis in their report, though, the Research Reviewers recognize the need to actively and meaningfully engage the public in discussion and education about research—particularly research they could potentially become involved in on a waiver of consent basis.

Below, we provide our appraisal of the reviews summarized above in Section 3, highlight key recommendations made by the reviewers, and describe Hennepin Healthcare's efforts to implement those recommendations and other process improvement initiatives.

a. Clinical Considerations

Since the outset of our review, we have been aware of concerns that Hennepin Healthcare EMS paramedic decisions in the field may have been influenced by (a) law enforcement suggestions, directions, or requests to use sedatives, and/or (b) the conduct of research at Hennepin Healthcare involving prehospital sedation. Both the Working Group and the Clinical Reviewers provided insights that are useful in assessing and addressing these concerns. As we understand the work of the Working Group and the Clinical Reviewers, neither identified evidence that Hennepin Healthcare EMS paramedics made different decisions about the use of sedation than they would have in the absence of law enforcement or research protocols.

OPCR Working Group. In our judgment, the Working Group conducted a complete and appropriate review of concerns directly arising from the OPCR draft report. In November 2018, we viewed selected footage from several of the BWC videos that had been reviewed by the

Working Group. Our assessment, based upon this limited review, was consistent with that of the Working Group. Specifically, we concluded that there were isolated episodes when paramedic professionalism did not meet expectations. We also concluded that the BWC footage that we viewed revealed no instance of inappropriate influence, or attempts to influence, by MPD of Hennepin Healthcare EMS paramedics in the exercise of their professional judgment. Though we did observe instances in which MPD officers made reference to Ketamine, we understood that Hennepin Healthcare EMS providers welcome all relevant input when they arrive on scene and would not cede their decision making regarding the use of sedation to MPD. Although MPD officers are now prohibited from suggesting or demanding the use of sedation pursuant to MPD Administrative Announcement AA18-03, such a policy was not in place at the time of the incidents discussed in the OPCR draft report.

In an effort to address these clinical considerations and act upon the insights provided by the Clinical Reviewers and Working Group, Hennepin Healthcare has:

- Increased quality assurance reviews from random sampling of prehospital sedation cases to mandatory review of all prehospital sedation cases. Hennepin Healthcare believes review of cases will ensure integrity of documentation, quality of clinical care, adherence to clinical guidelines, and will aid in the identification of trends that may lead to additional training and/or process improvement.

- Instituted a partnership with the National Alliance on Mental Illness ("NAMI") to provide Mental Health for First Responders training to all Hennepin EMS personnel. This training will include de-escalation techniques and provide additional tools for Hennepin Healthcare EMS personnel to use in the treatment of patients experiencing a mental health crisis.

- Scheduled implicit bias training for all Hennepin Healthcare EMS personnel that will lay the groundwork for Hennepin Healthcare EMS personnel to better understand the conditions that have led to fear and a lack of trust of first responders within communities of color by defining and identifying ways to combat implicit bias and committing to action in order to build trust between Hennepin Healthcare EMS and communities of color.

In addition to the above actions, we also encourage Hennepin Healthcare to consider prompt implementation of the following specific recommendations offered by the Clinical Reviewers and Working Group:

- Require that restraint devices and techniques that could impair respiration or circulation cease as soon as safely possible upon the administration of a sedative by Hennepin Healthcare EMS, and provide effective training to reinforce the same.

- Clarify and/or supplement policies, protocols, and guidelines applicable to the sedation of severely agitated patients and provide effective training to ensure all

Hennepin Healthcare EMS paramedics implement necessary patient monitoring when sedatives are administered.

- Understand and clarify roles and expectations for all personnel when Hennepin Healthcare EMS are called to a scene by law enforcement and provide effective training to reinforce the same.[8]

- Identify and provide the resources needed to ensure Hennepin Healthcare EMS engages robustly in comprehensive CQI.

Clinical Reviewers. Clearly, the Clinical Reviewers possess directly relevant, clinical expertise that aligned with the clinical questions Hennepin Healthcare sought to answer through independent expert review. Both Drs. Fowler and Williams—nationally respected in the field of emergency medicine—made valuable contributions by confirming that Ketamine use is a widely accepted intervention, within the standard of care, that can be safely employed by EMS professionals in the field. Dr. Williams also brought the unique perspective of his current work leading a community-based police oversight board and his personal experience as an emergency medical provider to police officers shot during the July 2016 ambush in Dallas. Dr. Williams was well-positioned to provide Hennepin Healthcare with insight regarding EMS/law enforcement interactions and meaningful community engagement.

The Clinical Reviewers' findings were primarily qualitative in nature. Dr. Fowler and Dr. Williams did not undertake a quantitative, retrospective examination of Hennepin Healthcare EMS use of Ketamine and other sedatives.[9] Accordingly, their work does not present data-based findings that resolve uncertainties regarding past use of Ketamine in the field, or whether such use was consistent with protocol(s) or influenced by research needs. Such an examination would require considerable time and resources (including extensive review of individual patient health records) that may be better invested in quality improvement measures going forward.

The Clinical Reviewers also discussed specific concerns involving the use of physical restraints (whether such restraints are used by law enforcement or EMS) on patients to whom EMS has administered a sedative. We have learned that some patients remain severely agitated after being physically restrained and that it can be dangerous for patients to struggle against restraints. To prevent such patients from developing a life-threatening form of severe metabolic acidosis, the current thinking in Emergency Medicine holds that EMS should intervene with rapid sedation.

[8] We specifically suggest that Hennepin Healthcare work to facilitate periodic, joint behavioral health emergency trainings in which Hennepin EMS and MPD participate in simulations. To the extent such trainings already occur, consider increasing their frequency. We also suggest that new Hennepin EMS paramedics participate in such trainings as soon as possible upon onboarding with the system.

[9] Among the questions initially included, but later withdrawn, from the tasks assigned to the Clinical Reviewers' was:

> Can you give an overall estimate of the percentage of cases, dating back to January of 2017, where Ketamine or another sedative was used appropriately for clinical reasons vs the percentage of cases where it was used inappropriately for non-clinical reasons?

The risk of severe metabolic acidosis was discussed and validated by the Clinical Reviewers. It would have been helpful if, in their written report, the Clinical Reviewers had addressed these specific observations within the context of a broader clinical discussion regarding restraint use.

In sum, additional input from the Clinical Reviewers will be useful to Hennepin Healthcare, and we understand that it will continue to work with them to identify opportunities for follow-up and future partnership.

b. Research

A detailed recitation of the sophisticated analysis provided by the Research Reviewers is beyond the scope of this Memorandum. However, we conclude that the Research Reviewers expertly identified and discussed several research regulatory issues that Hennepin Healthcare faces, including nuanced issues that arise as a result of the overlap of Common Rule and FDA regulations involving research with human participants.

While the efforts of the Research Reviewers were impressive, we note that the audit the Research Reviewers conducted was limited in scope. For example, the Research Reviewers' audit did not reach the actual conduct of the research (i.e., what happened in the field after the protocol received IRB approval). We believe this aspect of research is relevant to a fulsome review of the sedation concerns. Accordingly, we urge efforts to ensure that Hennepin Healthcare EMS paramedics acting as Research Assistants are consistently and effectively trained about involvement in research, and to ensure that Hennepin Healthcare EMS leadership is actively monitoring for potential patient care impacts related to participation in research.

In an effort to best utilize the insights provided by the Research Reviewers, Hennepin Healthcare is:

- Providing researchers and research personnel, IRB members, advisory board members, and administrators with additional professional education and training led by experts in human subject research ethics and regulations, on topics including study designs, types of applications, consenting, and regulatory changes.

- Redesigning and standardizing protocol templates for researcher-initiated studies to support a more uniform review of design, research-related interventions, study procedures, aspects of clinical care that are being altered because of study conduct, justification for conducting research in vulnerable populations, and consent procedures with justification for waiver of consent, if applicable.

- Creating tools that enhance IRB processes by supporting decision making and assisting the review and discussion of research protocols.

- Exploring a transition to an electronic system to provide comprehensive electronic submission and ongoing review of protocols to improve check-and-balance for the initial and continuing review of studies.

In addition, to echo a recommendation made by the Research Reviewers, Hennepin Healthcare should ensure that the training provided to Hennepin Healthcare IRB administrators, Hennepin Healthcare IRB members, and Hennepin Healthcare researchers specifically include: (1) differentiating between quality improvement activities, prospective observational studies, and comparative effectiveness research; and (2) understanding regulatory requirements for the waiver of documentation of informed consent.

c. Community Engagement

The Clinical Reviewers, Working Group, and Research Reviewers highlighted the importance of strengthening community engagement efforts. In response, Hennepin Healthcare has:

- Created a Public Research Advisory Board ("PRAB") that is representative of the communities that Hennepin Healthcare serves to advise researchers and the IRB, inform and engage our communities about ongoing research, and ensure that research is conducted in a culturally appropriate manner.

- Created a Community Advisory Board ("CAB") to connect the healthcare system to a diverse representation of consumers, caregivers, and community members to foster a better understanding of community needs and more effectively communicate the mission and work of Hennepin Healthcare to the community.

- Begun enhancing public communications about medical studies by sharing more information online, onsite in its facilities, and in person at public events in order to improve public awareness and community education about research.

These steps are directly responsive to reviewer recommendations. As Hennepin Healthcare builds these important community partnerships, we encourage the organization to ensure that its outreach educates the community about clinical research, generally, as well as specific studies Hennepin Healthcare plans to conduct and challenging research concepts including waiver of consent.

Conclusion

The use of Ketamine and other sedatives, including Haldol and Versed, by EMS to treat severe agitation in patients experiencing behavioral emergencies has been routine treatment within Hennepin County for a decade. Rapid sedation protects the patient and others on scene, while also creating an opportunity for EMS to provide other medical care the patient may urgently need and transportation to an appropriate facility. We expect that Hennepin Healthcare EMS paramedics will continue to rely on protocols and practices providing for the use of sedation to treat severe agitation in patients experiencing behavioral emergencies.

It is important to note that, as of the date of this Memorandum, we are aware of pending regulatory activity and litigation related to the sedation concerns. As these pending items unfold

and are resolved, we can envision that new questions may be raised, new areas for review may be identified, and additional rounds of community consultation and engagement may be warranted. Even so, we believe Hennepin Healthcare is engaging external stakeholders in a discussion of these issues and is prepared to move forward.