Hogan Lovells

MEMORANDUM
Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004
T +1 202 637 5600
F +1 202 637 5910
www.hoganlovells.com

TO Henry Parkhurst, J.D.
Assistant Hennepin County Attorney

FROM Heidi Gertner, J.D.
Partner
Hogan Lovells US LLP

Sara F. Goldkind, M.D., M.A.
Bioethics Consultant
Goldkind Consulting LLC

DATE November 1, 2018

Privileged And Confidential
Attorney-Client Communication
By Electronic Mail

SUBJECT Hennepin Healthcare System – Human Research Protection Regulatory Compliance; Final Audit Findings and Recommendations

---

I. Introduction

Hennepin Healthcare System, Inc. (Hennepin Healthcare) retained Hogan Lovells US LLP (which retained Goldkind Consulting LLC to consult on this project) to assess its Institutional Review Board's (IRB) review and approval of two sedation studies (Ketamine / Haloperidol, HSR #14-3841 and Ketamine / Midazolam, HSR #17-4306) and ten waiver of informed consent studies conducted at Hennepin Healthcare by Hennepin Healthcare employed physician-researchers (See Section IV.D. for a list of study names and file numbers) (hereinafter referred to as waiver of informed consent studies). The audit was performed to assess compliance with the U.S. Department of Health and Human Services' (DHHS) human subject protection regulations at 45 CFR

46, with the U.S. Food and Drug Administration's (FDA) human subject protection regulations at 21 CFR Parts 50 and 56, FDA's regulations governing the investigational use of drug and device products at 21 CFR Parts 312 and 812, Good Clinical Practice, and other best industry practices, including those described in federal guidance. In addition, Hennepin Healthcare requested written responses to seven specific questions about the conduct of the above-mentioned studies and related matters (See letter from H. Parkhurst, dated August 1, 2018, and email from H. Parkhurst dated August 13, 2018) (attached as Appendix 1).

This report provides findings from an on-site compliance audit (from August 7- 9, 2018), and a separate document-based review. The on-site audit focused mainly on the study design and initial IRB review and approval (including the risk assessment of the research-related activities and the application of the DHHS waiver provisions of informed consent) of the two sedation studies. Following the on-site audit, the audit team conducted a document-based review of the IRB files for ten waiver of informed consent studies. Also included in this final report are our recommendations for improvement. Our initial findings and analysis of the two sedation studies were provided to Hennepin Healthcare in the form of an Executive Summary (attached as Appendix 2).

This audit does not constitute a comprehensive evaluation of the conduct of the twelve reviewed studies after approval by the IRB. Furthermore, for the document based review of the ten additional waiver of informed consent studies, we did not conduct any interviews or review additional documentation apart from the IRB file. Moreover, this audit does not constitute a comprehensive evaluation of the functioning and regulatory compliance of Hennepin Healthcare's IRB. Through the audit process, we assessed some aspects of IRB regulatory compliance, discussed below. Other IRB-approved research conducted at Hennepin Healthcare or by Hennepin Healthcare staff were beyond the scope of this audit and were not reviewed.

II. Audit Methodology

From August 7-9, 2018, Heidi Gertner and Sara F. Goldkind (hereinafter referred to as "the audit team" "we" and "us") conducted an on-site compliance audit of Hennepin Healthcare's IRB that was limited to an analysis of the IRB's conduct and decision-making related to two sedation studies approved by the IRB under the DHHS regulations at 45 CFR 46.116(d) and FDA's regulations at 21 CFR Parts 50 and 56. The on-site audit consisted of reviews of the relevant IRB files (i.e., IRB study files for HSR #14-3841 and HSR #17-4306) including study protocols, some IRB written procedures, some aspects of IRB functioning, in-person interviews with several individuals associated with the sedation studies, and the review of numerous additional relevant documents (e.g., IRB study file for HSR #13-3682, relevant regulatory correspondence with FDA, and internal correspondence related to HSR #13-3682, and Hennepin County EMS System Advanced Life Support Protocols for the treatment of agitated individuals). The on-site audit took place at Hennepin Healthcare's Blue

Building, located at 900 South 8th St, Minneapolis, MN 55415. Following the on-site audit, we reviewed the IRB files of ten additional prospective waiver of informed consent studies that were on voluntary pause (See Section VI for a list of study names and file numbers).

A. Pre-On Site Audit Discussion and Preparation

During two telephone conferences, dated July 16 and July 19, 2018, several Hennepin Healthcare personnel, such as William Heegaard, and Karen Heim-Duthoy, and Assistant Hennepin County Attorney, Henry Parkhurst, described the scope of the review regarding the IRB and sedation studies, and provided relevant background information.

Additionally, we requested a wide range of documents to assist in the preparation for our audit, such as some of the IRB's Standard Operating Procedures (also known as written procedures), relevant IRB Review Checklists, the institution's Federal Wide Assurance, and IRB files related to the two sedation studies. Hennepin Healthcare provided all documents requested by the audit team.

B. In-Person Interviews and Group Meetings

The following individuals met with the audit team for in-person, on-site interviews:

- Karen Heim-Duthoy, Vice Chair of Hennepin Healthcare's IRB
- Dr. Fred Langendorf, Former Chair of Hennepin Healthcare's IRB
- Dr. Jeff Ho, Medical Director, Hennepin Healthcare EMS and Sedation Study Investigator
- Dr. Jon Cole, Hennepin Healthcare Physician and Sedation Study Principal Investigator
- Ross Chavez, Assistant Chief of Hennepin Healthcare EMS
- Wendy Lynch, Chief of Hennepin Healthcare EMS
- Dr. Brian Driver, Hennepin Healthcare Physician and Researcher and Sedation Study Investigator
- Dr. William Heegaard, CMO of Hennepin Healthcare
- Dr. Craig Peine, Current Chair of Hennepin Healthcare's IRB

Time was built into the schedule to allow for the option of in-person discussions with Hennepin Healthcare employees other than those referenced above. The audit team also participated in group meetings with Jon Pryor, CEO of Hennepin Healthcare, Lori Johnson, VP of Performance Improvement and Safety, Henry Parkhurst, Assistant County Attorney, Patti Jurkovich, Assistant County Attorney, Cheryl Ramsted, Chief External Relations Officer, Miaja Cassidy, Chief Compliance Officer, Mary Bergaas, VP of Operations of and Institutional Official, Hennepin Healthcare Research Institute, Kimberly Miller, Asst VP of Operations, Hennepin Healthcare Research Institute Don Lewis, Outside Counsel and Elizabeth Winchell, Outside Counsel.

C. Review of IRB Research Files and Related Documentation

The audit team requested and reviewed the complete files of the twelve IRB studies, including the sedation study files, and relevant IRB written procedures. These twelve studies all involved the DHHS waiver of informed consent at 45 CFR 46.116(d) or the waiver of documentation of informed consent under 21 CFR 56.109(c). Eleven of the reviewed studies were current studies (although all eleven had been voluntarily paused by the principal investigators due to community concerns). HSR 14-3841 (the Ketamine / Haloperidol study) was completed in 2016. For the sedation studies, we also reviewed internal Hennepin Healthcare email correspondence, Local EMS Advanced Life Support protocols, training materials for the research team including EMS personnel, and materials related to community consultation for an earlier version of the sedation study that was proposed but never approved and which forms the basis for the current sedation studies. As noted above, we also reviewed the IRB study files for another study (HSR# 13-3682), FDA correspondence with the principal investigator, and relevant internal Hennepin Healthcare correspondence.

D. Limited IRB Function Review

The audit team reviewed selected documents relevant to the functioning of the IRB, such as the IRB's written procedures (also referred to as standard operating procedures or SOPs), and other IRB administrative forms (such as IRB review checklists) to assess general regulatory compliance and proper, efficient function. In addition, in reviewing the twelve study files, we reviewed IRB meeting minutes, correspondence with investigators, and other relevant documents, such as documentation of investigators' human subject protection training completion. We also reviewed the institution's Federal Wide Assurance (FWA) and IRB Registration. Finally, we reviewed Hennepin Healthcare's documentation of its full accreditation by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). Hennepin Healthcare provided all requested documents to the audit team.

III. Relevant Regulatory Background

DHHS promulgated regulations, known as the Common Rule (45 CFR Part 46 Subpart A), that governs research involving human subjects supported, funded, or conducted by

DHHS.[1] FDA has also promulgated its own set of human subjects protections regulations (21 CFR Parts 50 and 56) that are generally applicable to clinical investigations regulated by FDA. The Common Rule and FDA's regulations include protections for human subjects participating in research, such as mandating IRB functions and operations, and the requirement, with few exceptions, to obtain informed consent from each human subject participating in research or the subject's legally authorized representative (LAR).

All federally-funded, conducted, or supported research must comply with 45 CFR Part 46; research that is FDA-regulated must comply with 21 CFR Parts 50 and 56 and other applicable FDA regulations governing investigational products at 21 CFR Parts 312 and 812. DHHS' Office for Human Research Protections (OHRP) oversees the administration of 45 CFR Part 46, and FDA oversees the administration of FDA-regulated research under its Bioresearch Monitoring (BIMO) Program.

Further, also at issue for this audit is the DHHS waiver provision at 45 CFR 46.116(d) and the expedited review regulations at 21 CFR 56.110 and 45 CFR 46.110. Similarly, the regulations governing exceptions from documentation of informed consent at 21 CFR 56.109(c) are relevant for some of the studies reviewed. In conducting the audit and analysis, we used these federal regulations and federally-issued guidance documents as a starting point for determining compliance and best practices within the research industry.

Under 45 CFR 46.103(a), an institution must have an FWA in order to receive DHHS support for research involving human subjects. Hennepin Healthcare has an FWA and voluntarily chose to extend the requirements and protections of 45 CFR Part 46 to non-federally supported research conducted within the institution. Additionally, federal regulations at 45 CFR 46.106 and 21 CFR 56.106 require each IRB in the U.S. designated under an FWA and IRBs that review FDA-regulated studies to register with the federal government. On its face, Hennepin Healthcare's IRB registration is current and appears to be accurate.

IV. Important Points and Observations

A. Hennepin Healthcare's IRB

Overall, based on this review, the IRB appears to have a complete set of written procedures, well-designed templates and checklists governing various aspects of IRB functioning and operations, follow appropriate review criteria, is well-organized with appropriate documentation, an up-to-date FWA and IRB registration, and is duly constituted. We also noted a high level of professionalism by all IRB personnel we interviewed and noted the same in all IRB communications we reviewed. The former

[1] Eighteen other federal agencies have either adopted their own set of regulations identical to the Common Rule or apply 45 CFR 46, Subpart A.

and current IRB Chairs and the Vice Chair also displayed a serious commitment to reviewing clinical research in accord with regulatory requirements and industry standards. Thus, the IRB appears to be functioning in compliance with the regulatory requirements at 21 CFR Parts 50 and 56 and 45 CFR Part 46. As mentioned earlier, Hennepin Healthcare is accredited by AAHRPP.

B. Comparative Effectiveness Research

Based on our limited review, we note that Hennepin Healthcare physician-researchers engage in efforts to evaluate and contribute to evidence-based medicine, conducting several comparative effectiveness studies. The sedation studies and some studies reviewed in the documentation based audit involve comparative effectiveness research of standard of care interventions, evaluating FDA-approved treatment or diagnostic options. Comparative effectiveness research on standard of care interventions is widely endorsed as a critically important method of advancing evidence-based medicine.[2]

It is important to note in the evaluation of these studies that the intellectual and regulatory discourse surrounding research evaluating standard of care interventions is evolving and complex. OHRP states in its federal guidance that there are differing views in the scientific, ethics, and research communities about the proper understanding and disclosure of foreseeable risks in standard of care research.[3] Meeting the medical needs of acutely ill individuals with emergent conditions in the pre-hospital setting, such as the sedation studies at issue, adds another layer of complexity in how to properly design and conduct such research and protect the individuals involved.

C. Two Sedation Studies

By way of summary background, with more detail provided throughout this audit report, Dr. Jon Cole was the principal investigator on two studies each comparing two FDA-approved drug products for the treatment of agitation in the pre-hospital setting. The studies were designed to evaluate time to adequate sedation after administration of drug products used to treat agitation under local standards of care; that is, they were designed to contribute to evidence based medicine. One study was conducted in 2014-2015 and the other began in 2017 and was ongoing until voluntarily paused by the principal investigator in June 2018, following community concerns regarding these and other studies involving waiver of informed consent. As part of both studies, EMS personnel, when encountering severely and profoundly agitated patients in the

---

[2] Institute of Medicine Report, Initial National Priorities for Comparative Effectiveness Research. Washington, DC. Institute of Medicine, 2009.

[3] OHRP, Draft Guidance, Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care, issued October 20, 2014, accessed at: https://www.hhs.gov/ohrp/regulations-and-policy/requests-for-comments/draft-guidance-disclosing-risk-in-standards-of-care/index.html.

community, would assess their need for drug therapy for sedation and if needed, drug therapy would be administered. The drug products administered for sedation (Ketamine, Haloperidol, and Midazolam) were part of Hennepin Healthcare's standard of care for the treatment of agitated patients in the pre-hospital setting, although the products are not specifically labeled for this use. We note that the use of these medications for in-field sedation of agitated patients is part of the local Advanced Life Support protocols, which include multiple other ambulance services. In addition, use of these drug therapies for preferential initial treatment for agitation was determined by randomizing subjects in 6-month blocks of time, although EMS personnel had the discretion to use the drug therapy they thought was most appropriate.

The study related procedures involved the use of a stop watch to accurately measure the time from administration of a sedative to adequate patient sedation, an agitation scale called the Altered Mental Status Scale (AMSS), and a data collection form. EMS personnel were instructed to exclude from the studies obviously pregnant women and persons who were obviously minors, persons to be transported to hospitals other than Hennepin Healthcare, and anyone else based on their medical judgment. Of note, severely and profoundly agitated patients whether enrolled in the study or not, were treated with the same choice of medical therapies available on the ambulance.

Both of the studies were approved by the IRB using the expedited review procedures. The IRB considered the studies to involve no more than minimal risk to the subjects and to qualify for the DHHS waiver of informed consent under 45 CFR 46.116(d). The IRB also required the subjects, post-enrollment, to be given a Notification of Enrollment form. Below are our general observations of the principal investigator's and the IRB's conduct as it relates to these two studies.

- As explained in more detail below, the two sedation studies were mischaracterized by the investigator as prospective, observational studies, when in fact there were study-related interventions. We think the two sedation studies are more properly described as open-label, prospective, pragmatic, cluster-randomized,[4] comparative effectiveness studies involving lawfully marketed FDA-approved products used in accordance with the local EMS standard of care for the sedation of agitated patients in the pre-hospital setting. We do not think, however, that this mischaracterization of the studies as observational affected the overall safety, rights, and welfare of the individuals involved.

[4] Weijer C, Grimshaw JM, Taljaard M, et. al., *Ethical Issues Posed by Cluster Randomized Trials in Health Research,* Trials Journal (2011);12(100):1-11. These authors explain that cluster randomized trials are trials that randomize "intact social units, such as households, primary care practices, hospital wards, classrooms, neighborhoods and entire communities, to differing intervention arms. Research interventions in cluster trials may be directed at the entire cluster or at individual cluster members." In the sedation studies involving Ketamine, Haloperidol, and Midazolam, individuals receiving preferential initial drug therapy for the treatment of agitation for one 6-month block of time were compared to individuals receiving another preferential initial drug therapy for the treatment of agitation during another 6-month block of time.

- Overall, it is our view that the individuals enrolled in both studies were not exposed to any additional risk from being in the research as compared to the care they would have received had they not been enrolled. We do not believe the rights, safety, and welfare of these individuals were compromised by being enrolled in these studies. As an additional protection, the IRB required a Notification of Enrollment form be provided to individuals after their inclusion in these studies. The forms clearly indicated that participants could contact the principal investigators with their questions. For the Ketamine / Midazolam study, the Notice of Enrollment also allowed for subjects to withdraw their data from the study database.

- It is also our view that it was not possible for the investigators/EMS personnel to obtain informed consent from the subjects due to their medical condition (i.e. severe or profound agitation). It was also not possible to obtain consent from the subject's LAR typically due to lack of availability of the LAR and/or the rapidity with which treatment would need to be administered. We also do not believe that the waiver of informed consent exposed the individuals enrolled in the research to an unacceptable level of risk.

- Furthermore, it is our understanding that although the EMS protocols differentiated between severe and profound agitation, in practice, those distinctions are not binary and are based often times on very close, subjective judgment calls of the professional paramedics. In these studies the investigators used the AMSS instrument to characterize the level of agitation in their research findings. The use of the scale itself did not dictate whether a person received sedation nor whether an individual was enrolled in research.

- Based on the documentation reviewed and the interviews conducted, we believe that the principal investigator and all research personnel thought that the drug products used to treat agitation in the two sedation studies were considered by the local medical experts to constitute appropriate pharmacotherapy for severe and profound agitation. We note that the drug products at issue were considered part of their local standards of care to treat pre-hospital agitation as evidenced by the EMS clinical treatment protocols issued by the local EMS Board. Thus, severely and profoundly agitated individuals received the same care whether they were enrolled in the studies or not. Further, in accordance with the precautions listed in the Ketamine and Midazolam labels, the EMS personnel involved in the studies had the proper experience, equipment, and training in airway maintenance and control of respiration and the control of hypersalivation.

- In response to our inquiries, the principal investigator, the EMS medical director, and the EMS personnel explained that during the conduct of these studies, the EMS personnel were clearly instructed to use their discretion to

determine the proper medical care of the individuals involved, including which drug products, if any, to administer for the treatment of agitation, as well as whether or not it would be appropriate for an individual patient to be enrolled in or excluded from these studies. It was also explained by the EMS medical director and EMS personnel that the EMS protocols are essentially treatment guidelines designed to assist EMS personnel in terms of how they handle various medical and emergency situations. We were told they are not to be interpreted as proscriptive or determinative. Furthermore, the treatment guidelines can be modified via email or other communication medium by the EMS medical director, as dictated by state statute.[5] The EMS medical director altered the EMS protocols during the time of the conduct of these studies as an administrative matter regarding which drug product would be preferentially administered for pre-hospital agitation during each cluster randomized block, and to describe the use of the stop-watch, the AMSS, and data collection.

- Moreover, the principal investigator, the EMS medical director, and EMS personnel explained that repeated instructions were provided to EMS personnel that no one should be treated for sedation if such treatment was unwarranted clinically. That is, no one should be sedated for their agitation for the sake of enrolling them in the research.

- We have not identified serious or continuing non-compliance[6] in the design of the sedation studies or in their review and approval by the IRB which would represent regulatory violations that would require reporting to either FDA or OHRP. To explain further, we do not believe that during the design, review and approval of these studies there were significant, severe, numerous, or an alarming pattern of regulatory violations that would support a finding that the research subjects under the care of the investigator(s) would have been exposed to unreasonable and significant risk of illness or injury or that the subjects' rights, safety and welfare would have been seriously compromised.

- We do not consider any mistakes made by the principal investigator in designing and describing the studies and by the IRB in reviewing and approving the studies to rise to the level of causing unexpected serious harm to subjects[7] that would require suspension or termination[8] of the IRB-approved research under either DHHS or FDA regulations.

---

[5] 2017 Minnesota Statute 144E.265, Subd.2.

[6] Compliance Program Guidance Manual, Clinical Investigators: https://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm133773.pdf. Compliance Program Guidance Manual, IRBs: https://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm133768.pdf.

[7] 21 CFR 56.113.

D. Ten Additional Waiver of Informed Consent Studies

Out of an abundance of caution, in the summer of 2018, the investigators of ten additional prospective studies being conducted at Hennepin Healthcare using a waiver of informed consent under 45 CFR 46.116(d) or a waiver of documentation of informed consent under 21 CFR 56.109(c), voluntarily paused their studies, in order to evaluate the studies' designs, the IRB's determinations, and regulatory compliance. These studies are:

1. HSR# 18-4521: Prospective Observational Investigation of Olanzapine / Midazolam for Treatment of Acute Undifferentiated Agitation in the Emergency Department

2. HSR# 18-4488: Brain Tissue Oxygenation in Sepsis-Associated Delirium

3. HSR# 17-4432: Drug Order for Rapid Sequence Intubation in Emergency Department Intubation

4. HSR# 17-4414: The National Heads Up CPR Registry

5. HSR# 17-4331: In-patients Suspected of Having Acute Cardiogenic Pulmonary Edema in the Emergency Department, Using Lung Point of Care Ultrasound-Are There Significant Differences in the Quality of Images Obtained with Different Probes When Evaluating for Pulmonary Edema

6. HSR# 17-4288: Cerebral Oximetry Monitoring Using Near-Infrared Spectroscopy During Adult Procedural Sedation-A Pilot Study

7. HSR# 16-4248: Suspected CO Poisoning in Emergency Department Patients-A Prospective Observational Trial

8. HSR# 16-4118: Detecting Cerebrovascular Autoregulation with Directed Information Measure

9. HSR# 15-4062: Ultrasound Confirmation of Aortic Balloon Placement during REBOA

10. HSR# 12-3487: In-Market Safety Surveillance of Laundry Detergent Using Poison Control Center Data

---

[8] We note that the Ketamine / Haldol study was already completed at the time of this audit. The Ketamine / Midazolam study was voluntarily paused by the principal investigator prior to this audit. We have recommended elsewhere that after revisions are made to the study protocol that it be re-reviewed by the full IRB prior to proceeding.

These studies involve a variety of study designs ranging from drug and device comparative effectiveness research to registry studies. We were asked to conduct a document-based review of these studies.

Overall, we had some concerns with the protocol submissions and the IRB's decisions related to these studies. Many of the IRB submissions for these studies were in the form of a "summary protocol." These summaries typically were missing information important for proper consideration by the IRB. Further, it was typically challenging, based on the summary protocols, to ascertain what were protocol-driven, study-related interventions and what were considered standard of care interventions that would have occurred clinically regardless of the study. Next, often there was no description of study-related interventions and procedures, the total number of subjects needed for study enrollment, statistical analysis plans, and justifications for use of the waiver of informed consent. Further, the submissions were not well organized or precisely described. Often the IRB would seek clarifications but did not appear to request a complete protocol submission or challenge the investigators' characterizations of the studies.

V. Analysis of the Two Sedation Studies

The regulatory and ethical analysis of the two sedation studies is complex and requires a thorough discussion of several inter-related considerations, such as whether an investigational new drug application (IND) was required, the applicability of the DHHS waiver of informed consent, the appropriateness of expedited review, and the level of the research-related risks associated with the studies. This analysis was focused on the investigator's initial submissions to the IRB and the IRB's analysis and review of those submissions.

A. IND Exemption Related Considerations

One critical issue in the analysis of regulatory compliance with these two studies is whether an IND was required under FDA's regulations at 21 CFR Part 312 to conduct the studies. At 21 CFR 312.2(b), FDA's regulations describe the six criteria that must be met for a clinical investigation of a marketed drug to be exempt from the IND requirements. For example, the exemption from needing an IND is appropriate if 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 CFR 312.2(b)(iii). In the case of the sedation studies, the investigators involved and the IRB determined that the use of the drugs in these studies was essentially in accord with their approved labeling (albeit for a different indication), and that their use in these studies did not significantly increase the risk or decrease the acceptably of the risks. In addition, all other criteria at 21 CFR 312.2(b) were met, including the fact that there was never any intention to submit the data to FDA in support of a new indication for use nor to support any other significant changes in the labeling or advertising of the studied drugs. 21 CFR 312.2(b(i) and (ii).

Our finding that the IND exemption criteria were met is bolstered by a letter from the Director of the Division of Psychiatry Products at the Center for Drug Evaluation and Research (CDER) dated April 10, 2014, which stated that the Agency found that a trial studying Ketamine / Haloperidol (HSR #13-3682)[9] in the pre-hospital setting to evaluate time to sedation in agitated patients was IND exempt. We note that this study was very similar in design to the two sedation studies at issue here. Further, the patient population described in the IND application for the Ketamine / Haloperidol trial (HSR #13-3682) was identical to the patient populations studied in the two sedation studies. Thus, the investigator and the IRB concluded the use of the marketed drug products did not alter the risk calculus and no IND was needed.

Another relevant criterion to meet the exemption is that the study must comply with FDA's human subjects protections regulations at 21 CFR Parts 50 and 56.[10] As a technical regulatory matter, 21 CFR Part 50 was not followed by Hennepin Healthcare's IRB because the use of the DHHS waiver of informed consent is not applicable to FDA-regulated clinical investigations (i.e. there are no waiver of informed consent provisions in 21 CFR Part 50 and obtaining consent is required for each subject or the subject's LAR). However, FDA, in 2017, issued an enforcement discretion guidance[11] describing its intention to not object to an IRB waiving or altering informed consent requirements for certain minimal risk clinical investigations that are important to address public health needs and that do not compromise the rights, safety, or welfare of human subjects. It is our understanding that this guidance was issued as an interim measure while FDA promulgates regulations that reflect the statutory authority granted to FDA by the 21st Century Cures Act, which permits an exception from the informed consent requirements for such clinical trials.[12] Thus, the exemption from the IND requirements should not be invalidated due to technical noncompliance with 21 CFR Part 50's informed consent requirement.

---

[9] It should be noted that IND for the Ketamine / Haloperidol study (HSR #13-3682) was withdrawn from FDA and the study was never initiated.

[10] 21 CFR 312(b)(iv).

[11] FDA Guidance, IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects, issued July 2017, accessed at: https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM566948.pdf.

[12] On December 13, 2016, the 21st Century Cures Act (Cures Act) (P.L. 114-255) was signed into law. Title III, section 3024 of the Cures Act amended sections 520(g)(3) and 505(i)(4) of the FD&C Act to provide FDA with the authority to permit an exception from informed consent requirements when the proposed clinical testing poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety, and welfare of the human subject. The "Cures Act" can be accessed at: https://www.gpo.gov/fdsys/pkg/PLAW-114publ255/pdf/PLAW-114publ255.pdf.

B. Hennepin Healthcare's IRB's Use of the DHHS Waiver of Informed Consent

As the IRB applied the DHHS waiver of informed consent for these studies, the next critical point of the analysis is whether the regulatory criteria for use of the DHHS waiver of informed consent were met. 45 CFR 46.116(d) lists four criteria that must be met for the waiver of informed consent: a) the research involves no more than minimal risks to the subjects; b) the waiver will not adversely affect the rights and welfare of the subjects; c) the research could not practicably be carried out without the waiver; d) whenever appropriate the subjects will be provided with additional pertinent information after participation.

As discussed below, we believe the two sedation studies involved no more than minimal risk. The only study related interventions involved the use of a stop watch to evaluate time to sedation after drug administration, a standardized agitation assessment scale, and a data collection form.[13] Next, given that the study participants would have received the same treatment in the pre-hospital setting whether or not they were enrolled in the study, we do not believe that the rights and welfare of the subjects were adversely affected by the use of the waiver. Because the participants were agitated and needed urgent intervention by EMS personnel, they could not have provided meaningful informed consent to participate. Similarly, subjects' LAR's were not typically available to provide consent and/or the rapidity with which treatment must be administered precluded the ability to obtain informed consent. Therefore, the research could not practicably have been carried out without the waiver. Last, the subjects were provided with additional pertinent information after enrollment that is not required under federal regulations but is frequently required by Hennepin Healthcare's IRB.

C. Expedited Review

In this instance, the sedation studies were reviewed by the IRB using the expedited review procedure (instead of review by the full board) and were approved. We note that when using the expedited review procedures an IRB must still consider the approval criteria under 21 CFR 56.111 and 45 CFR 46.111, and in these instances Hennepin Healthcare's IRB found and documented that the approval criteria were met. Under the federal regulations at 21 CFR 56.110 and 45 CFR 46.110, an IRB can expedite review for certain kinds of research involving no more than minimal risk (whether the studies involved minimal risk is discussed below). There are seven expedited review categories for initial review. In this instance the IRB chose to exempt these studies using Category 5, research involving materials that have been collected, or will be collected solely for non-research purposes. We think this categorization was incorrectly chosen because

[13] See OHRP's guidance referenced in footnote 2 regarding the reasonably foreseeable risks in research evaluating the standard of care, and FDA and DHHS' list of categories of research eligible for IRB expedited review procedures. Expedited Review Category 1a makes clear that such clinical investigations would be considered minimal risk studies by both FDA and DHHS.

some data were collected solely for research purposes. However, assuming this study was a minimal risk, we think that Category 1a (research on drugs for which an IND is not required) and/or 4 (research involving collection of data through noninvasive procedures) could have been chosen to expedite this study. In addition, we note that OHRP's IRB expedited review criteria permit use of the waiver of informed consent for studies that are IND exempt.[14] Thus, assuming these studies involved no more than minimal risk, it is our opinion that they met the criteria for the use of the IRB's expedited review procedures.

D. Minimal Risk

The next part of the analysis is whether these studies were appropriately considered to be minimal risk studies, defined by regulation as "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."[15] This determination is relevant for both whether these studies were able to be reviewed using the IRB's expedited procedures and whether the DHHS waiver of informed consent was appropriately applied.

As noted above, the principal investigator and the IRB believed that the study-related interventions involved: 1) the use of a stop watch to accurately measure the time to sedation after administration of the sedative; 2) the use of the AMSS to assess the individual's level of agitation; and, 3) the collection of various data points. They did not consider the administration of the drugs for sedation or the cluster randomization (six months of preferential use of each drug) to be study-related interventions. This determination led them to conclude that the incremental risks of the study interventions, as compared with the risks of the treatments that the individuals would have received as patients in the pre-hospital setting, involved no more than minimal risk. It is our view that this is an appropriate interpretation of the regulations for several reasons described below.

- The informed consent regulations at both 45 CFR 46.111(a)(2) and 21 CFR 56.111(a)(2) state that "risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research) …."

---

[14] See expedited review categories at: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/categories-of-research-expedited-review-procedure-1998/index.html.

[15] See 21 CFR 50.3(k) and 45 CFR 46.102(j).

- OHRP issued a draft guidance document in 2014 on disclosing reasonably foreseeable risks in research evaluating standards of care.[16] In this document OHRP explains its position that, "in general the *reasonably foreseeable risks of research* in a study include the already identified risks of the standards of care being evaluated as a purpose of the research when the risks being evaluated are different from the risks some of the subjects would be exposed to outside of the study." OHRP further clarifies that if the research is designed to evaluate the risks of the standards of care or to ascertain the existence, extent or nature of a particular harm then those risks should be disclosed. In contrast, the sedation studies were designed such that the risks individuals were exposed to as part of the studies were no different from the risks they were exposed to from treatment outside the research; and, although data about any complications of medication use were collected in these studies, the primary outcome of each study was time to adequate sedation. Hence, based on OHRP's guidance, we believe that the drugs themselves should not be considered study-related interventions, and therefore the risks of these studies should be determined only on the basis of the limited minimal risk study interventions (i.e., use of a stop watch and the AMSS, and data collection).

- Furthermore, the Secretary's Advisory Committee on Human Research Protections (SACHRP) made recommendations on regulatory issues in cluster randomized studies on October 26, 2016.[17] In its letter to the Secretary of DHHS, SACHRP opines that comparative effectiveness research utilizing a cluster randomized design can meet the definition of a minimal risk study depending on whether each individual subject will face potentially the same risks he or she would face without research enrollment. As previously articulated, we believe that this is indeed true for the sedation studies.

- Next, the list of studies eligible for expedited IRB review procedures (a list applicable to both FDA and DHHS-regulated research) includes a category that permits "research on drugs for which an investigational new drug application (under 21 CFR Part 312) is not required". This category also states, "research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review." The clear implication of Expedited

[16] OHRP Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care, can be accessed at: https://www.hhs.gov/ohrp/regulations-and-policy/requests-for-comments/draft-guidance-disclosing-risk-in-standards-of-care/index.html

[17] SACHRP's recommendations on regulatory issues in cluster randomized studies can be accessed at: https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-b-november-2-2016-letter/index.html.

Review Category 1a is to permit comparative effectiveness studies of FDA-approved products, in which the clinical investigation does not significantly increase the risks (or decrease the acceptability of the risks) associated with the use of the drug product(s). Moreover, Expedited Review Category 1a makes clear that such clinical investigations would be considered minimal risk studies by both FDA and DHHS. Analyzing FDA and DHHS IRB approval criteria (45 CFR 46.111(a)(2) and 21 CFR 56.111(a)(2)) and the criteria for IRB expedited review, we believe that the risks of the study interventions in the sedation studies as compared to the risks of the treatments that individuals would have received as patients in the clinical setting, should be considered to represent no more than minimal risk.[18]

- Further, some prominent thought leaders in this space maintain that five factors need to be considered in determining whether a randomized, controlled trial poses no more than minimal risk.[19] They are: 1) whether genuine clinical equipoise exists (that is, there is genuine uncertainty within the expert medical community about the preferred treatment);[20] 2) all of the treatment options included in the research study fall within current standard of care; 3) there is no currently available treatment with a more favorable risk-benefit profile than the treatments included in the study; 4) the nontherapeutic components of the research are safely under the minimal risk threshold; and 5) the research protocol provides sufficient latitude for treating physicians to individualize care when appropriate. For reasons previously discussed, we believe that all five of these criteria were satisfied by the sedation studies, and therefore the incremental risk associated with these studies can reasonably and appropriately be designated as no more than minimal risk.

Another, more conservative interpretation of the regulatory requirements and in accord with our understanding of some prior determinations by FDA and OHRP, would consider the risks of the treatments in a study (when the treatments are directed by the protocol) to be research-related risks. For these studies, cluster randomization in 6-month blocks was used to identify one drug or the other as the preferential initial treatment for pre-hospital agitation. If the use of the drug products were considered part of the research interventions, this would mean that the foreseeable risks of Ketamine, Midazolam and Haloperidol would need to be factored into the overall risk calculation of the study. Under this interpretation, these studies would have been considered to present greater than minimal risk and would not have been eligible for expedited review or the DHHS waiver of informed consent. Even under this more conservative viewpoint,

---

[18] Joffe S and Wertheimer A, *Determining Minimal Risk for Comparative Effectiveness Research,* The Hastings Center: IRB Ethics & Human Research May-June 2014;36(3):16-18.

[19] Morris MC and Nelson RM, *Randomized, Controlled Trials as Minimal Risk: An ethical analysis,* Critical Care Medicine 2007;35(3):940-944.

[20] Friedman B, *Equipoise and the Ethics of Clinical Research,* New England Journal of Medicine 1987;317:141-145.

we do not believe the rights, safety, and welfare of the individuals enrolled in these studies were compromised by their participation. For the reasons discussed above, we do not agree with this interpretation.

E. Additional Comments on the Two Sedation Studies

1) Availability of Haloperidol on the Ambulances

While the EMS clinical treatment protocol (and not the studies themselves) did alter the availability of Haloperidol on the ambulances, all three drug products at issue, along with others, were considered by local medical experts to constitute appropriate pharmacotherapy for severe and profound agitation. Nowhere is it required by law or hospital policy to have all approved medical therapies or all therapies that fall within the standard of care provided to all patients at all times by a health care provider. Institutions make decisions about what to offer patients at any given time based on cost, efficacy, safety, and other factors. Further, the change to the EMS protocol to remove Haloperidol from the ambulances was not specific to the studies; instead, the drug was not available to pre-hospital agitated patients whether or not they were enrolled in the studies.

2) The Use of the AMSS

The use of the AMSS did not cause EMS personnel to consider more patients to be severely and profoundly agitated. As explained above, the EMS providers were trained to make a clinical judgment on whether or not to treat the patient with sedatives based on their level of agitation, and not the AMSS score. Sedation was not to occur unless clinically indicated under normal paramedic practices at all times. The EMS treatment protocols which defined severe and profound agitation were used as guidelines to inform the EMS technician's thinking, but were not binding or proscriptive. During the study itself, the EMS personnel would use their clinical judgment, including consideration of the EMS treatment protocols, to decide whether a given patient was appropriate for sedation therapy.

The patient's rating on the AMSS, a graded ordinal scale (which was subjective in nature) was then used as a research tool to help the investigators describe the level of agitation in their findings, and to assess the time to adequate sedation, the study's primary outcome measure. The AMSS was implemented simply to standardize measurement of the patients' level of agitation after the decision to sedate. The use of the scale itself did not dictate whether a person received sedation, nor whether the patient was enrolled in the research. Therefore, no patients were exposed to any increased risks by its use.

VI. Analysis of Ten Additional Waiver of Informed Consent Studies

Our review of the ten additional waiver of informed consent studies yielded numerous specific findings (see Section IV.D.), however, below we list some recurrent concerns.

- In several protocols involving comparative effectiveness research, the investigators did not consistently distinguish treatment interventions involving the clinical standard of care from research-related interventions, including manipulations of the standard of care for research purposes. This confusion resulted in the investigators mischaracterizing their comparative effectiveness research involving study-related interventions as prospective, observational studies, when in fact there were research-related interventions that should have been considered when assessing the risk level of the research. In turn, the IRB relied on the investigator's characterizations and thus may not have been able to properly evaluate the approval criteria, the risk level of the interventions, and may have led to the IRB choosing an improper expedited review category.

- Next, the IRB did not consistently ask the investigators to include in their protocols a justification for their request for the IRB to waive informed consent. Not having this information, in some instances, led to the IRB granting the waiver when some subjects or their LAR were available and able to provide informed consent. In such circumstances, the IRB should, but did not, ask the investigators to justify the need for the waiver of informed consent. That is, the investigators should have been required to explain why the research could not practicably be carried out without the waiver of informed consent.

- Furthermore, the IRB did not consistently identify the correct category under which to expedite IRB review; did not identify research activities that are exempt from 45 CFR Part 46 Subpart A; and, did not consistently make (and document) the required significant risk (SR), non-significant risk (NSR) device determination at a fully convened IRB meeting.

VII. Responses to Seven Specific Questions

1. Does the sedation IRB study involving Ketamine and Midazolam (Versed) and related protocol meet regulatory standards?

The answer to this question is long and complex and involves an evaluation of various issues related to the design and description of the study in the summary protocol, along with an analysis of the risk level of the research-related interventions, the IND exemption related considerations under 21 CFR 312.2(b); the IRB review procedures;

and, the use of the DHHS waiver of informed consent under 45 CFR 46.116(d). Our analysis is provided below.

As noted above, although the summary protocol submitted had notable flaws in its drafting, and the IRB did not require a full protocol and chose an incorrect expedited review category, we do not think subject safety was compromised or subjects were harmed (none received any different medical care) as a result of their participation in the study.

Study design and summary protocol description

A proper understanding of the research-related interventions has a significant impact on the assessment of the risk level of the study, whether the study qualifies for IRB expedited review (and which expedited category is appropriate), and in turn the acceptability of the DHHS waiver of informed consent. With this in mind, as mentioned above, the Ketamine / Midazolam study for the treatment of agitation in the pre-hospital setting was described by the investigator and approved by the IRB as a prospective, observational study. The protocol summary describes the study interventions of the use of a stop watch, the use of the AMSS, and the recording of research-related data on a data collection form. The protocol summary, however, was unclear in its description of research-related activities; it did not describe whether the drug products used to treat agitated patients by the EMS personnel were study interventions. Therefore, the study is not accurately described as a prospective, observational study. Rather, based on the actual study design, we believe the study would more properly be described as an open-label, prospective, pragmatic, cluster-randomized, comparative effectiveness study involving lawfully marketed FDA-approved drug products used in accordance with Hennepin Healthcare's local standard of care for the sedation of agitated patients.

Risk level of research-related interventions

Based on our separate interviews with the principal investigator, the EMS medical director, EMS personnel, and the IRB, it is our understanding that they believed the study-related interventions involved: 1) the use of a stop watch to accurately measure the time to sedation after administration of the sedative; 2) the use of the AMSS to assess the individuals' level of agitation; and 3) the collection of various data points. They did not consider the administration of the drugs products for the treatment of sedation or the cluster randomization (six months of preferential use of each drug) to be study-related interventions. This determination led them to appropriately conclude that the incremental risks of the study interventions, as compared with the risks of the treatments that the individuals would have received as patients in the clinical setting involved no more than minimal risk.

In addition to clarifying the intentions of the principal investigator, we have carefully reviewed FDA and DHHS informed consent regulations, DHHS guidance on disclosure of reasonably foreseeable risks in research evaluating standards of care, FDA guidance

on its enforcement discretion policy on IRB waiver or alteration of informed consent for clinical investigations, and other materials, and we believe that the drugs and their associated risks should not be considered study-related interventions. Therefore, the risks of the study should be determined only on the basis of the limited study interventions (i.e., use of the stopwatch, use of the AMSS, data collection), making this a minimal risk study.

Alternatively, another interpretation of the regulatory requirements could lead to the conservative conclusion that the risks of the treatment drugs, when the treatments are given in accordance with the protocol (i.e. cluster randomization in 6-months blocks was used to identify one drug or the other as the preferential initial treatment for agitation) are research-related risks. This view would make this study greater than minimal risk (a determination that would not permit use of the IRB expedited review procedures and the use of the DHHS waiver of informed consent). We do not concur with this assessment.

IND exemption considerations

One important issue to analyze is whether this study met the regulatory requirements for an IND exemption under 21 CFR Part 312. At 21 CFR 312.2(b), FDA's regulations lay out the six criteria that must be met for a clinical investigation of a marketed drug to be exempt from the IND requirements. One criterion, for example, to meet the exemption from needing an IND is that 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 CFR 312.2(b)(iii). In this instance, the investigators and the IRB correctly determined that the use of the drugs were essentially in accord with their approved labeling, and that their use in this study did not significantly increase the risk or decrease the acceptability of the risks. In addition, all other criteria at 21 CFR 312.2(b) were met, including the fact that there was never any intention to submit the data to FDA in support of a new indication for use nor to support any other significant changes in the labeling or advertising of the studied drugs. 21 CFR 312.2(b)(i) and (ii).

Next, while FDA's regulations on informed consent, 21 CFR Part 50, do not currently contain waiver provisions for informed consent similar to those under 45 CFR 46.116(d), we believe that the human subjects involved in this study were all appropriately protected. In this instance, the IRB did not require informed consent from the individuals enrolled in the research, but rather, waived informed consent under 45 CFR 46.116(d). While it could be argued that the application of the DHHS waiver to FDA regulated but IND exempt research violates FDA's regulatory requirements, the waiver determination is in accordance with FDA's current enforcement discretion policy and direction from Congress. The IRB further protected the subjects enrolled in this study by requiring the investigators to provide them, when possible, pertinent information about the study and gave subjects the opportunity to contact the principal investigation with questions or in the case of the Ketamine / Midazolam study to opt-out of the research.

IRB review procedures

Under FDA's regulations at 21 CFR 56.110 and DHHS's regulations at 45 CFR 46.110, an IRB can review research under expedited procedures for certain kinds of research involving no more than minimal risk. There are seven expedited review categories for initial review. In this instance the IRB chose to exempt this study using Category 5, research involving materials that have been collected, or will be collected solely for non-research purposes. We think this categorization was incorrectly chosen; however, assuming this study was a minimal risk, we think that Category 1a (research on drugs for which an IND is not required) and/or 4 (research involving collection of data through noninvasive procedures) could have been chosen to expedite this study.

Waiver of informed consent considerations

In our view, Hennepin Healthcare's IRB appropriately applied the waiver of informed consent under 45 CFR 46.116(d) for this study and was justified in not obtaining informed consent from the individuals enrolled or their LARs. These regulatory provisions list four criteria that must be met for the waiver of informed consent: a) the research involves no more than minimal risks to the subjects; b) the waiver will not adversely affect the rights, safety, and welfare of the subjects; c) the research could not practicably be carried out without the waiver; d) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

In this study, the research involved no more than minimal risk as explained above. Next, given that the individuals enrolled in the study would have received the same treatment, provided at the professional discretion of the Hennepin Healthcare EMS personnel, in the pre-hospital setting whether or not they were enrolled in the study, we do not believe that the rights, safety, and welfare of the subjects were adversely affected by the use of the waiver. Moreover, EMS personnel had the discretion in the choice of hospitals to transport patients for care. Because the individuals were severely or profoundly agitated and needed urgent intervention by EMS personnel, they could not have provided meaningful informed consent to participate. Therefore, the research could not practicably have been carried out without the waiver. Last, the subjects were provided with additional pertinent information after enrollment.

2. **Are there any portions of the IRB study and protocol that failed applicable standards for research?**

We think there were aspects of the summary protocol that were deficient due to imprecise drafting and the omission of pertinent information. The principal investigator mischaracterized the study as observational, did not clearly delineate in the protocol summary the study-related interventions, and, did not develop and submit to the IRB for review a comprehensive protocol.

Similarly, some aspects of the IRB's review and approval were not optimal. The IRB did not require submission of a comprehensive protocol (e.g. the inclusion of a statistical analysis plan and a justification for the waiver of informed consent); it relied on the investigator's inaccurate description of the study's design; and their reliance on the investigator's description of the study resulted in the IRB expediting review under the incorrect category.

3. Was the designated type of waiver of consent appropriate for this study?

Under a technical reading of FDA's regulatory requirements, the answer is no. The IRB's use of the DHHS waiver was not appropriate for this study because FDA's regulations do not allow for a waiver of informed consent. However, as explained above, we think the IRB's use of the DHHS waiver of informed consent under 45 CFR 46.116(d) was justified in this instance based on FDA's recent enforcement discretion guidance and direction from Congress in the 21st Century Cures Act. See response to question 1 and section 4 above for a more complete analysis of this issue.

4. In your review of our current waiver of consent studies, did you find any concerns, errors or areas of improvement?

In addition to the two sedation studies, we conducted a records-based review of the ten additional, current Hennepin Healthcare studies where the IRB waived informed consent under the DHHS waiver or waived the documentation of consent under FDA's regulations. Our review did yield areas of concern, errors, and areas for improvement.

Overall, we note that the physician-investigators at Hennepin Healthcare tried to contribute to evidence-based emergency medicine by conducting comparative efficacy studies in a very challenging space. Many of these studies involved enrollment of individuals with impaired ability to provide informed consent for themselves secondary to their disorders/conditions (a vulnerable population), and who are in need of emergent or urgent medical care. For many of these conditions, the drug products often used are not well-studied for these conditions and circumstances and may be used in medical practice and research for non-labeled uses. This practice is not unique to Hennepin Healthcare.

That said, we note that many submissions to the IRB for the ten waiver of informed consent studies were in "summary" form and were not complete, resulting in the omission of important information (such as a description of study-related interventions and procedures, the total number of subjects needed for study enrollment, statistical analysis plans, and justifications for use of the waiver of informed consent). In some instances, the IRB sought clarifications from the investigators, but did not appear to request a complete protocol submission. Without a complete protocol, it is challenging for any IRB to fully assess the criteria for approval, such as whether subject selection is equitable, the risks are minimized, and that risks are reasonable in relation to the anticipated benefit. See 21 CFR 56.111 and 45 CFR 46.111.

In addition, we identified several recurrent concerns with the waiver of informed consent studies. They are:

- Investigators consistently had difficulties distinguishing treatment interventions involving standard of care from research-related interventions involving manipulations of standard of care for research purposes. This confusion resulted in the investigators' mischaracterizing comparative effectiveness research involving study-related interventions as prospective, observational studies or as quality improvement activities. Because these studies did involve the use of research-related interventions, those interventions should have been considered when the IRB assessed the risk level of the research. This assessment of the level of risk affects the IRB's analysis of the study's eligibility for the IRB's expedited review procedures, including which category to choose, and the appropriate use of the waiver of informed consent.

- While the investigators did use the IRB's checklist indicating they had met the DHHS criteria for the waiver of informed consent, in most cases, the protocols themselves did not contain an explanation or justification for why informed consent could not be obtained and how the study met the criteria. Similarly, the IRB did not consistently ask the investigators for a justification for the waiver of informed consent. We even noted some circumstances where the waiver of informed consent was requested by the investigator and approved by the IRB when some subjects or their LARs were available and able to provide informed consent. Ideally, each protocol would contain a justification, and when submissions to the IRB lack such a justification, the IRB should ask investigators to revise the protocol accordingly. Without this information, the IRB is at a disadvantage when trying to apply the waiver criteria.

- For these studies, the IRB did not consistently: identify the correct category under which to expedite IRB review (when appropriate); did not identify research activities exempt from 45 CFR part 46 Subpart A; and, did not consistently make (and document) the required SR / NSR device determination at a fully convened IRB meeting.

5. Can you suggest improvements or changes to our IRB process and suggest ways to enhance community engagement in our IRB process?

Although the IRB has compliant written procedures, is well-organized, and is appropriately constituted, we do think there are areas for improvement for both the IRB and Hennepin Healthcare physician-investigators. Furthermore, while the regulations

do not require community consultation[21] for studies where the IRB has waived informed consent, we suggest several ways Hennepin Healthcare can positively engage with the community it serves about its research.

Suggested improvements and changes to the IRB process

Based on our assessment of Hennepin Healthcare IRB's review and approval of the two sedation studies, and the ten additional waiver of informed consent studies, we have several suggestions for improvements and changes to the IRB's submission and review processes:

- We recommend instituting a standard protocol template that includes all elements necessary to completely and accurately describe the proposed research. This template will allow more uniform review of study submissions and will eliminate "summary" protocol submissions by investigators and acceptance by the IRB. With a complete protocol, the IRB will better be able to assess the regulatory criteria for approval at 21 CFR 56.111 and 45 CFR 46.111. The required use of protocol templates[22] by the IRB would likely help improve:

    - The IRB administrators' and IRB members' understanding of the studies submitted, including but not limited to their design (e.g., prospective observational, interventional, no more than minimal risk, greater than minimal risk), the research-related interventions, study procedures, and the aspects of clinical care that are not being altered because of study conduct;

    - Efficiency and effectiveness of IRB review of study submissions and the ability to make the appropriate regulatory determinations regarding what is considered minimal risk, what qualifies for expedited review, exemption decisions, and evaluation of the 45 CFR 46.111 and 21 CFR 56.111 criteria; and,

    - Investigators' understanding of the need to provide detailed information to the IRB for their study submissions, and the accuracy and completeness of their submissions.

[21] We note that studies conducted under FDA's exception from informed consent for emergency research at 21 CFR 50.24 do require community consultation.

[22] There are many protocol templates available on the internet for use by Hennepin Healthcare System's IRB. One such rich resource we is found at: https://irb.research.chop.edu/protocol-templates.

Further, as a matter of policy, the IRB should only review complete submissions that follow the protocol template.

- We recommend providing training to all IRB administrators and members on the following:
    - Differentiating between quality improvement activities, prospective observational studies, and comparative effectiveness research;
    - Understanding which research is eligible for use of the IRB expedited review procedures and selecting the appropriate expedited review category based on the characteristics of the research;
    - Implementing regulatory compliant procedures for determining SR/NSR device determinations;
    - Differentiating between clinical research that is exempt from 45 CFR Part 46, Subpart A (the "Common Rule") and research that is no more than minimal risk and eligible for the use of IRB expedited review procedures; and,
    - Understanding regulatory requirements for the waiver of documentation of informed consent under 21 CFR 56.109(c)(1) and (2).

Suggestions for improvements or changes to enhance community engagement

While there is no requirement to engage with the community about the research we reviewed, i.e. the sedation studies and other waiver of informed consent studies, we advise Hennepin Healthcare to make concerted efforts to enhance their community engagement efforts. Such efforts lead to more transparency and understanding about research generally and emergency research more specifically. Creating and nurturing a partnership of this sort between Hennepin Healthcare and the community it serves is a laudable and valuable goal.

"Community engagement" can have several meanings. For example, a minimum level of community engagement involves having a community or non-affiliated member(s) on the IRB to represent community interests and perspectives. The regulations require, and Hennepin Healthcare's IRB has, a community/non-affiliated member on the IRB. At another extreme is what is known as community-based participatory research (CBPR) in which there is "a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. CBPR begins with a research topic of importance to the community and has the aim of

combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities."[23]

We recommend a middle ground of sorts based on our discussions with Hennepin Healthcare's senior management for studies where the IRB has waived informed consent. This would involve developing a more robust, direct process of reaching out to the community to create partnerships between Hennepin Healthcare and the local community. These efforts could involve the physician-investigators, EMS personnel, other components of Hennepin Healthcare, patient advocacy groups, community-based organizations, and the like. This suggestion is in line with the DHHS' Secretary's Advisory Committee on Human Research Protections' (SACHRP) recommendation that institutions, IRBs, and investigators consider "whether it would be appropriate to perform community outreach to provide knowledge to the affected population of the existence of research [involving cluster randomized trials]. This does not substitute for informed consent from individuals but may be respectful of autonomy in those cases where the IRB has made the finding that the research meets the regulatory criteria for waiver of approval."[24]

To enhance community engagement for studies involving the waiver of informed consent (or even clinical research more generally), we think Hennepin Healthcare should:

- Make efforts to become familiar with and to make itself known to various community groups that regularly utilize its services;
- Be sensitive to and account for any relevant historical experiences and community groups may have developed towards research (e.g., mistrust);
- Make efforts to foster trust between Hennepin Healthcare research staff and community members;
- Share its research goals with the community (i.e. how the research would address the medical needs of community groups), share overall research results (not necessarily individual results) with community groups, and facilitate two-way communication;

---

[23] Flicker S, Travers R, Guta A, McDonald S, and Meagher S, *Ethical Dilemmas in Community-Based Participatory Research: Recommendations for Institutional Review Boards* Journal of Urban Health: Bulletin of the New York Academy of Medicine 2007;10.1007;s11524-007-9165-7.

[24] SACHRP Recommendations on Regulatory Issues in Cluster Randomized Studies, October 26, 2016, available at: https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-b-november-2-2016-letter/index.html.

- Provide educational materials for individuals and communities to better understand clinical research;

- Make efforts to build the capacity of community groups to better understand what clinical research is, how it addresses the health needs of community groups, and the procedures involved in research;

- Place a special emphasis in its outreach on educational efforts on informed consent processes, the waiver or alteration of informed consent and when it is acceptable to be used from ethical and regulatory perspectives;

- Foster and encourage transparency in its communications with the community; and,

- Hone its abilities to identify and conduct research that addresses the needs of the community groups it serves.[25]

To implement these goals, we recommend a two-pronged approach to community engagement. The first involves educating the community about research so they are knowledgeable about its importance, the processes involved, and their rights as research participants. The second is to educate the community and seek input about specific clinical trials Hennepin Healthcare is planning to conduct in order to increase awareness and support involvement by the community.

We recommend these community engagement activities be part of an on-going effort which has a broad reach. Hennepin Healthcare could conduct a series of meetings with various community groups to discuss the ongoing and planned research with the opportunity for community input and expressions of any concerns. Hennepin Healthcare could develop a variety of educational materials or use pre-existing materials from the National Institutes of Health, for example, such as posters, an on-line slide show, and pamphlets for distribution in various community settings and within the hospital. Other outreach opportunities would include radio announcements, newspaper articles, and "meet and greets." Further, for research directed to potential subjects with a specific disease or condition, Hennepin Healthcare could conduct outreach to specific patient advocacy groups and disease-based organizations.

We also recommend engaging in some community-based activities and service projects such as street fairs, truck touches, and other fun events where the Hennepin Healthcare staff and community members could interact. Such activities can go a long way towards integrating Hennepin Healthcare into the community and fostering a strong sense of connectedness and building trust.

---

[25] Shore N, *Re-Conceptualizing the Belmont Report: A Community-Based Participatory Research Perspective* Journal of Community Practice (2006);14(4):5-26.

6. **Are any of the sedative drugs (Ketamine, Midazolam, Haloperidol) approved for use in the prehospital environment or is being used "off label"? Are there any implications that we should be aware of when using these medications as "off label"?**

Ketamine, Midazolam, and Haloperidol are all not labeled for use for treating agitation in the pre-hospital setting. However, as lawfully approved and marketed drug products, FDA allows physicians to prescribe products "off label" to patients within the practice of medicine. Similarly, FDA allows research on lawfully approved and marketed drug products for non-labeled uses without needing an IND if certain criteria are met. See 21 CFR 312.2(b).

Although the drug products used in the sedation studies were used for a non-labeled use, it is our understanding their use in the prehospital setting for agitation constituted the local standard of care at Hennepin Healthcare and we do not believe subjects were harmed in any way due to their enrollment. Individuals enrolled in trials evaluating Ketamine / Haloperidol and Ketamine / Midazolam for the treatment of agitation received the same care whether they were enrolled in the study or not. Next, in accordance with the precautions listed in the Ketamine and Midazolam labels, the EMS personnel involved in the study had the proper experience, equipment, and training in airway maintenance and control of respiration.

It is also our view that the route of administration, dose, patient population or other factors did not significantly increase the risks (or decrease the acceptability of the risks) associated with the use of the drug products in these two studies in comparison to current labeling for these products. Further, an IRB determined that the criteria for approval were met for these studies, including that the risks to subjects were minimized, risks to subjects are reasonable in relation to anticipated benefits, and selection of study subjects was equitable.

7. **Additional question (provided by Henry Parkhurst, Assistant County Attorney, email dated August 13, 2018): In review of the waiver of consent studies that are currently on hold, do you believe there should be a suspension of the holds or do you have other recommendations regarding the studies on hold?**[26]

We think it was prudent for the investigators to initiate a voluntary pause the eleven studies listed in Section IV.D. and to conduct an independent analysis of the IRBs determination that the criteria for the waiver were met. As explained above, most all of the protocols could be improved with more careful drafting and the inclusion of pertinent information. Overall, we think the IRB should require revisions to the protocols and resubmission for review by the fully convened board before proceeding.

26

We do think, however, that one study can be resumed without revisions. This is because we think that HSR #17-4414, "The National Heads Up CPR Registry," is actually exempt from 45 CFR 46, Subpart A. This study involves the collection of de-identified data only, and therefore would not require ongoing IRB review and approval or the application of the waiver of informed consent. See 45 CFR 46.101(b)(4). Further, for this study, it is our opinion that it would be ethically acceptable to use the data collected to date. We do recommend that the fully convened IRB review the study to determine if it agrees with our assessment that the study is exempt and about the use of the data. The IRB should then document its findings in its meeting minutes.

It is our opinion that the remaining ten waiver of informed consent studies should continue to be paused until: a) the IRB confirms with each principal investigator that he/she would like to resume the study; b) the IRB requests revisions to the studies (e.g., the study designs, descriptions, and informed consent procedures) that appropriately clarify the research; and, c) the fully convened IRB reviews the revised submissions, to determine that they satisfy all criteria for IRB approval of research under the applicable regulations (e.g., 21 CFR 56.111, 45 CFR 46.111), that the waiver of informed consent is ethically justified, and that the waiver of informed consent, as applied to each study, meets the requirements of 45 CFR 46.116(d). All IRB findings and pertinent discussions should be documented in the IRB meeting minutes, including required SR and NSR determinations for device studies. Further, the IRB should discuss and document whether data previously collected in these studies can be used by the investigators from an ethical and scientific perspective. We think that for most of the studies it would be appropriate to use the data as the use of the waiver did not affect the rights, safety, and welfare of the subjects and the data collected would be considered scientifically valid.

We recommend that investigators revise their submissions to make clear relevant information such as what the study interventions are, what the standard of care is, what the justification for the waiver of informed consent is, and how subjects will be protected in the research. And, although several of these studies will meet the criteria for using the IRB expedited review procedures, we believe a cautious approach would be for each of these studies to be considered and discussed by the fully convened IRB. All IRB determinations and findings should be documented in its meeting minutes.

* * *

Recommendations for Improvement

Overall, we found Hennepin Healthcare's IRB to be generally compliant with FDA and DHHS regulations and to be well-functioning. We do, however, based on the limited scope of our review, have various suggestions for improving regulatory compliance and strengthening Hennepin Healthcare's human research protection program.

With regard to the two sedation studies and the ten additional waiver of informed consent studies, above we noted a number of missteps made in the design of the studies by the principal investigators and in their review and approval by the IRB. Thus, we recommend:

- The required use of a standardized protocol template by all investigators for every submission to the IRB, and rejection by the IRB of all submissions which do not follow the template and/or are otherwise incomplete. Among other elements such as the purpose of the study, the procedures involved in the study, and a background section containing a scientific justification for the research, all submissions should clearly identify:
    - the research design,
    - the research-related interventions (as opposed to standard of care),
    - the inclusion and exclusion criteria,
    - a statistical analysis plan,
    - a justification for conducting the research with vulnerable populations (if applicable), and
    - an explanation of the informed consent procedures and/or a justification for a waiver.
- Supplemental training for IRB administrators and IRB members along with all investigators on topics where we noticed some confusion such as:
    - Differentiating between quality improvement activities, prospective observational studies, and comparative effectiveness research;
    - Understanding which research is eligible for use of the IRB expedited review procedures and selecting the appropriate expedited review category based on the characteristics of the research;

- Implementing regulatory compliant procedures for determining SR/NSR device determinations;

- Differentiating between clinical research that is exempt from 45 CFR Part 46, Subpart A, and research that is no more than minimal risk and eligible for the use of IRB expedited review procedures; and,

- Understanding regulatory requirements for the waiver of documentation of informed consent under 21 CFR 56.109(c)(1) and (2).

- Community engagement efforts as noted above in response to question 5.

Appendix 1: Letter and Email from H. Parkhurst re scope of review

Appendix 2: Executive Summary