

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER

250 Marquette Ave, Ste. 600  
Minneapolis, MN 55401  
(612) 334-4100 Fax: (612) 334-4134

DATE(S) OF INSPECTION

8/7/2018-8/23/2018\*

FEI NUMBER

2127118

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

[REDACTED]

FIRM NAME

Human Subjects Research Committee

STREET ADDRESS

Hennepin County Medical Center, ,  
Hennepin Healthcare System, Inc.; 914 S 8

CITY, STATE, ZIP CODE, COUNTRY

Minneapolis, MN 55404-1204

TYPE ESTABLISHMENT INSPECTED

Institutional Review Board

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

**DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:**

**OBSERVATION 1**

The IRB approved the conduct of research, but did not determine that informed consent would be sought from each prospective subject or the subject's legally authorized representative, to the extent required by 21 CFR 50.

Specifically, the IRB approved studies for waiver of consent under 45 CFR 46.116 without determining the informed consent requirements of 21 CFR 50; and, that do not appear to meet the criteria for exception from informed consent (21 CFR 50.23) nor emergency research (21 CFR 50.24). Examples:

IRB#	Study title	Approval date	Review type	Study status
[REDACTED]	Ketamine vs. Haloperidol for Severe Agitation in the Prehospital Setting	7/10/2014	Expedited	Closed 7/1/2016
[REDACTED]	Ketamine versus Midazolam for Prehospital Agitation	5/11/2017	Expedited	Paused 6/25/2018
[REDACTED]	Prospective Observational Investigation of Olanzapine versus Haloperidol versus Ziprasidone versus Midazolam for the Treatment of Acute Undifferentiated Agitation in the Emergency Department	5/22/2017	Expedited	Closed 5/1/2018
[REDACTED]	Prospective Observational Investigation of Olanzapine Versus Midazolam for the	5/29/2018	Expedited	Paused 7/16/2018

**SEE REVERSE  
OF THIS PAGE**

EMPLOYEE(S) SIGNATURE

Sharon L Matson, Investigator  
Kellie L Thommes, Investigator

Sharon L Matson  
Investigator  
Signed By: Sharon L Matson -S  
Date Signed: 08/23/2018 10:46:44

X

DATE ISSUED

8/23/2018

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 250 Marquette Ave, Ste. 600 Minneapolis, MN 55401 (612)334-4100 Fax: (612)334-4134	DATE(S) OF INSPECTION 8/7/2018-8/23/2018* FEI NUMBER 2127118
---	---

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED [REDACTED]
--

FIRM NAME Human Subjects Research Committee	STREET ADDRESS Hennepin County Medical Center, , Hennepin Healthcare System, Inc.; 914 S 8
CITY, STATE, ZIP CODE, COUNTRY Minneapolis, MN 55404-1204	TYPE ESTABLISHMENT INSPECTED Institutional Review Board

Treatment of Acute Undifferentiated Agitation in the Emergency Department			
--	--	--	--

**OBSERVATION 2**

The IRB approved the conduct of research in a situation where some or all of the subjects were likely to be vulnerable to coercion or undue influence, but did not determine that additional safeguards had been included in the study to protect the rights and welfare of those subjects.

Specifically, the IRB has approved studies that are identified as including a Vulnerable Subjects category "impaired ability to give informed consent" without evidence of determining additional safeguards had been included in the study to protect the rights and welfare of those subjects. Examples are noted above under Observation 1.

**OBSERVATION 3**

The IRB used an expedited review procedure for research which did not appear in an FDA list of categories eligible for expedited review, and which had not previously been approved by the IRB.

Specifically, requests that do not meet the criteria for expedited review have been given expedited approval. Examples:

**A. Requests for emergency use (EU) of experimental or investigational products:**

IRB#	Product requested	FDA#	EU request date	Approval date	Date of use	Report date
[REDACTED]	Epicel CEA	HDE #BH990200	6/2/2017	6/2/2017	Not used	6/9/2017
[REDACTED]	Hemopure	eIND 17705	9/1/2017	9/1/2017	9/2-4/2017	9/12/2017
[REDACTED]	Epicel CEA	HDE# BH990200	11/6/2017	11/6/2017	11/27/2017	12/1/2017

<b>SEE REVERSE OF THIS PAGE</b>	EMPLOYEE(S) SIGNATURE Sharon L Matson, Investigator Kellie L Thommes, Investigator	DATE ISSUED 8/23/2018
	<div style="text-align: right;"> <small>Sharon L Matson Investigator Signed By: Sharon L Matson -S Date Signed: 08-23-2018 10:40:44</small>  X </div>	

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER

250 Marquette Ave, Ste. 600  
Minneapolis, MN 55401  
(612) 334-4100 Fax: (612) 334-4134

DATE(S) OF INSPECTION

8/7/2018-8/23/2018\*

FBI NUMBER

2127118

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

[REDACTED]

FIRM NAME

Human Subjects Research Committee

STREET ADDRESS

Hennepin County Medical Center, ,  
Hennepin Healthcare System, Inc.; 914 S 8

CITY, STATE, ZIP CODE, COUNTRY

Minneapolis, MN 55404-1204

TYPE ESTABLISHMENT INSPECTED

Institutional Review Board

[REDACTED]	Hemopure	eIND 18016	2/17/2018	2/17-18/2018	2/17-18/2018	2/19/2018
[REDACTED]	Hemopure	eIND 18357	7/12/2018	7/12/2018	7/12/2018	7/12/2018

**B. IRB study**

[REDACTED] using a new unapproved non-invasive [REDACTED] presented by the sponsor and clinical investigator as nonsignificant risk (NSR), and requesting waiver of signed consent, approved via expedited review 11/18/2016.

**OBSERVATION 4**

The IRB has no written procedure for conducting its initial and continuing review of research.

Specifically, there are no written procedures governing:

A. Determination of additional safeguards for the IRBs Vulnerable Subjects category "impaired ability to give informed consent".

B. Creation, maintenance, or use of the database utilized for tracking all studies and activities of the IRB.

**\*DATES OF INSPECTION**

8/07/2018(Tue), 8/08/2018(Wed), 8/10/2018(Fri), 8/15/2018(Wed), 8/16/2018(Thu), 8/21/2018(Tue), 8/22/2018(Wed), 8/23/2018(Thu)

Kellie L Thommes

Investigator

Signed By: Kellie L. Thommes-S

Date Signed: 08-23-2018 10:48:18

X

**SEE REVERSE  
OF THIS PAGE**

EMPLOYEE(S) SIGNATURE

Sharon L Matson, Investigator  
Kellie L Thommes, Investigator

DATE ISSUED

8/23/2018

Sharon L Matson

Investigator

Signed By: Sharon L. Matson-S

Date Signed: 08-23-2018 10:45:44

X

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."

**Administration**

701 Park Ave.  
Minneapolis, Minnesota  
55415-1829

Tel: 612-873-3000

www.hcmc.org



September 14, 2018

Michael Dutcher, DVM  
Director  
Minneapolis District Office  
U.S. Food and Drug Administration  
250 Marquette Avenue, Suite 600  
Minneapolis, MN 55401

**Delivered via email & courier**

**Re: Response to Inspectional Observations; FEI Number 2127118**

Dear Director Dutcher:

Between August 7 and August 23, 2018, FDA Investigators Sharon L. Matson and Kellie L. Thommes performed an inspection of Hennepin County Medical Center's Institutional Review Board (IRB), which is part of Hennepin Healthcare System, Inc.'s (Hennepin) human research protection program. Upon completion of the inspection, Ms. Matson and Ms. Thommes issued a Form FDA 483, with four inspectional observations listed.

[REDACTED] I am writing on behalf of the institution to respond to each observation. As I hope this response demonstrates, we at Hennepin understand the importance of complying with applicable human subjects protections and clinical trial-related regulatory requirements and Good Clinical Practice generally, which safeguard both clinical trial subjects and data integrity. For that reason, we are committed to taking all action, where appropriate, to enhance those aspects of compliance raised by the inspectional observations.

**Observation #1**

The IRB approved the conduct of research, but did not determine that informed consent would be sought from each prospective subject or the subject's legally authorized representative, to the extent required by 21 CFR 50. Specifically, the IRB approved studies for waiver of consent under 45 CFR 46.116 without determining the informed consent requirements of 21 CFR 50; and, that do not appear to meet the criteria for exception from informed consent (21 CFR 50.23) nor emergency research (21 CFR 50.24). Examples: Studies [REDACTED]

**Response to Observation #1**

We do not agree with Observation 1. As explained in detail below, for the studies noted in Observation 1, Hennepin's IRB determined that the waiver of consent under 45 CFR 46.116(d) was appropriate, and thus informed consent was not sought from each



prospective subject or the subject's legally authorized representative under 21 CFR Part 50. Importantly, FDA issued an enforcement discretion guidance in 2017<sup>1</sup> 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.<sup>2</sup> 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 21<sup>st</sup> Century Cures Act, which permits an exception from the informed consent requirements for such clinical trials.<sup>3</sup> As the studies noted in Observation 1 are all minimal risk studies, and met the criteria for a waiver of informed consent, the IRB acted appropriately in not requiring informed consent from the study participants.

Although not mentioned in the first observation, it is important to note that the studies listed in Observation 1 did not require an Investigational New Drug Application (IND) 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. For example, one criterion 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 these instances, the investigators and the IRB determined that the use of the drugs in these studies were essentially in accord with their approved labeling, and that their use in these studies 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

---

1 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>

2 We believe it is worth noting that the regulatory and scholarly discourse surrounding informed consent for research evaluating standard of care interventions, such as those studies listed in Observation 1, is evolving and complex. Comparative effectiveness research on standard of care interventions, appropriate disclosures of foreseeable risks, the risk levels, and ethically acceptable informed consent procedures for such research are all current topics of intense debate. As part of the federal efforts to facilitate evidence-based medicine through comparative effectiveness research, in 2014 the Department of Health and Human Services issued draft guidance, "Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care". 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> This guidance supports the IRB's determination that the reasonably foreseeable risks associated with the marketed drugs used in the studies identified by FDA in Observation 1 as standard of care were not considered research related risks.

3 On December 13, 2016, the 21<sup>st</sup> 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>

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 to the Hennepin investigator 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 proposed trial studying Ketamine v. Haloperidol [REDACTED] 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 all of the studies noted in Observation 1. Further, the patient population described in the IND application for the Ketamine v. Haloperidol [REDACTED] was the same as the patient populations studied in all of the trials listed in Observation 1. Thus, the investigator and the IRB concluded the use of the marketed drug products in the studies listed in Observation 1 did not alter the risk calculus and an IND was not required.

Next, while 21 CFR 312.2(b)(iv) requires an investigator to comply with FDA's human subject protection regulations at 21 CFR Parts 50 and 56 to be eligible for the IND exemption, we believe the human subjects involved in the trials noted in Observation 1 were all appropriately protected. In these instances, as described above, the IRB did not require informed consent from the participants, but rather waived informed consent under 45 CFR 46.116(d). This waiver determination is in accordance with FDA's current enforcement discretion policy. The IRB further protected the subjects enrolled in all of these studies by requiring the investigators to provide them, whenever possible, pertinent information about the trials and gave subjects the opportunity to opt-out of the research.

Moreover, the IRB appropriately applied the waiver of informed consent under 45 CFR 46.116(d) for the studies noted in Observation 1. 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, 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 these studies, the research involved no more than minimal risk. For example, in [REDACTED] 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.<sup>4</sup> Next, given that that the study participants would have received the same treatment, provided at the professional discretion of Hennepin Emergency Medical Service 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, Emergency

---

<sup>4</sup> 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.

Medical Service personnel had discretion in the choice of hospital to transport patients for care. Because the participants were agitated and needed urgent intervention by Emergency Medical Service 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.

Based on the foregoing, Hennepin's IRB appropriately applied the waiver of informed consent under 45 CFR 46.116(d) for these studies, and was justified in not obtaining informed consent from the study participants or their legally authorized representatives.

### **Corrective Action Plan for Observation #1**

- We acknowledge that the protocols for the studies referenced in Observation 1 could have been written more clearly to, among other aspects of the trial, explain that the standard of care was not considered a research related intervention. Therefore, we plan to draft and implement a protocol template for investigators to use to help ensure accurate and complete descriptions of a study prior to submission to the IRB for review and approval.

### **Observation #2**

The IRB approved the conduct of research in a situation where some or all of the subjects were likely to be vulnerable to coercion or undue influence, but did not determine that additional safeguards had been included in the study to protect the rights, safety, and welfare of those subjects. Specifically, the IRB has approved studies that are identified as including Vulnerable Subjects category "impaired ability to give informed consent" without evidence of determining additional safeguards had been included in the study to protect the rights, safety, and welfare of those subjects. Examples are noted above under Observation 1.

### **Response to Observation #2**

We do not agree with Observation 2. We believe Hennepin's IRB protected vulnerable populations who would enroll in the approved research in Observation 1, and implemented additional safeguards to protect the rights, safety, and welfare of those subjects. Hennepin takes very seriously its obligation to provide additional safeguards to subjects likely to be vulnerable to coercion or undue influence. For example, the IRB attends to these considerations routinely, in part evidenced by the fact that it has standing members who are sufficiently qualified through experience, expertise, and diversity to safeguard the rights, safety, and welfare of vulnerable subjects. See 21 CFR 56.107(a). Specifically, specialties represented in the composition of the IRB include an obstetrician/gynecologist, pediatrician, neuropsychologist, community representative, and someone with prison system expertise. Further, the IRB has developed specific written procedures for additional protections for vulnerable populations (i.e., Subpart B, Subpart C, and Subpart D).



Most importantly, however, to respond to Observation 2 directly, when a waiver of informed consent is applicable under 45 CFR 46.116(d), the regulations do not require supplementary safeguards beyond the safeguards that are already incorporated into the four criteria for the waiver of informed consent. We note, however, that Hennepin's IRB imposed additional safeguards by requiring both notification of enrollment to subjects and an opt-out procedure.

Additionally, the protocols themselves for the studies noted in Observation 1 were designed to essentially exclude specific vulnerable populations. For example, the protocol for study [REDACTED] required that obviously pregnant women, persons who were obviously minors, and those known to be under 18 or pregnant be excluded from the study. Because the patient population involved agitated persons in need of urgent drug therapy, it was impossible to confirm pregnancy status and proof of age, and therefore some vulnerable subjects may have been enrolled. However, because the drug therapy involved the standard of care for Hennepin, any vulnerable subjects who were enrolled received the same drug therapy they would have received outside the study. Therefore, the subjects, whether considered part of a vulnerable population or not, were not exposed to any study interventions that were considered more than minimal risk.

### **Corrective Action Plan for Observation #2**

- We acknowledge that the study protocols reviewed by the IRB for the studies noted in Observation 1 could have been drafted to more clearly explain the inclusion / exclusion criteria, as well as the protections for vulnerable populations. Therefore, the protocol template mentioned above that we are developing will require clear exclusion and inclusion criteria and specifically address the protections for vulnerable populations.
- Because we are highly committed to the protection of human subjects enrolled at our institution, we are revising our IRB's Standard Operating Procedures and IRB checklists to further ensure consideration of appropriate safeguards for vulnerable populations, including those with an impaired ability to provide informed consent.

### **Observation #3**

The IRB used an expedited review procedure for research which did not appear in an FDA list of categories eligible for expedited review, and which had not previously been approved by the IRB. Specifically, requests that do not meet the criteria for expedited review have been given expedited approval.

A) Requests for emergency use of experimental or investigational products  
(Examples: [REDACTED])

B) IRB study [REDACTED] using a new [REDACTED]

unapproved non-invasive [REDACTED] presented by the sponsor and clinical investigator as nonsignificant risk, and requesting waiver of signed consent, approved via expedited review 11/18/2016.

### **Response to Observation #3**

- A) We appreciate the FDA highlighting Observation 3A for us. We note that the investigators in studies [REDACTED] timely notified the IRB regarding the emergency use of the experimental or investigational drug products. The IRB promptly confirmed receipt of the notification to each investigator and in the confirmation, the word "approve" was used, instead of the word "confirm." The word choice "approve" instead of "confirm" resulted in studies [REDACTED] falling into the category of expedited review and approval.

For study [REDACTED] we acknowledge that the investigator's report to the IRB was received 6 working days from the date of use. We acknowledge the 5 working day timeline specified in 21 CFR 56.104.

- B) We appreciate FDA highlighting Observation 3B for us. While the IRB did make a non-significant risk determination for study [REDACTED] this determination was made through the use of the expedited review procedures and was not made by the full IRB committee as required under 21 CFR Part 812 and recommended in FDA guidance.<sup>5</sup> We note that the IRB appropriately considered the study as qualifying for expedited review and could have approved it using the expedited procedures, but only after the full board (or FDA) made the significant / non-significant risk determination.

### **Corrective Action Plan for Observation #3A**

- We have developed a form for the IRB to use in order to ensure the correct term, "confirm," is used in response to an investigator's notification of the emergency use of experimental or investigational products.
- To prevent the delay in investigator reporting, we plan to train our research staff on the requirement to report within the 5 working day time period and implement the use of a new form for the investigators to report the emergency use of a test article to the IRB.

### **Corrective Action Plan for Observation #3B**

- We plan to revise SOP #4 and Hennepin's Checklist for IND/IDE Status to reflect that all device risk determinations must be made by the full IRB committee when no FDA determination has previously been made.

---

<sup>5</sup> See guidance issued by FDA's Center for Devices and Radiological Health and the Office of Good Clinical Practice's titled "Significant Risk and Non-significant Risk Medical Device Studies," January 2006.

- We note that the study specifically described in Observation 3B is currently inactive. Upon any request to restart the study, the full IRB will make a risk determination for the device study.

#### **Observation #4**

The IRB has no written procedure for conducting its initial and continuing review of research. Specifically, there are no written procedures governing:

- A) Determination of additional safeguards for the IRB's Vulnerable Subjects category "impaired ability to give informed consent";
- B) Creation, maintenance, or use of the database utilized for tracking all studies and activities of the IRB.

#### **Response to Observation #4**

- A) We do not agree with observation 4A. 21 CFR 56.108(a) and (b) contain four specific IRB functions and operations that must be included in IRB written procedures. One of those specific requirements is to have a procedure for conducting its initial and continuing review of research. 21 CFR 56.108(a)(1). Hennepin, in fact, has met this regulatory requirement by having detailed written procedures for conducting its initial and continuing review of research (see SOP #4 (Initial Review of Research) and SOP #5 (Review of Previously Approved Research)).

The Form FDA 483 states that Hennepin does not have written procedures governing the determination of additional safeguards for vulnerable subjects with "impaired ability to give informed consent." We note that the regulations do not require IRBs to have written procedures, incorporated in its written procedures for initial and continuing review, related specifically to vulnerable populations. FDA's own guidance<sup>6</sup> specifically states that its regulations "allow flexibility in both format and content of written procedures, which gives IRBs the ability to establish procedures best suited to their own operations."<sup>7</sup> We note, however, that Hennepin's IRB does have several SOPs and checklists that reference safeguards for vulnerable populations.

- B) We do not agree with observation 4B. The Form FDA 483 mentions that the IRB does not have IRB written procedures describing the creation, maintenance, or use of a database utilized for tracking all studies and activities of the IRB. We note that such a written procedure is not a regulatory requirement. We also note, however, that Hennepin's IRB maintains a well-functioning database that is

---

6 FDA's Guidance, IRB Written Procedures: Guidance for Institutions and IRBs, accessed at: <https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm512761.pdf>

7 FDA's Guidance, IRB Written Procedures, p.3.

complete, accurate, and accessible that provides routine reports for day-to-day IRB record keeping and operations. Further, the IRB also keeps securely stored paper files on-site (for current studies) and off-site (for studies  $\geq$  3 years after study closure or termination). Therefore, no corrective action regarding observation 4B is planned.

#### **Corrective Action Plan for Observation #4A**

- Although not a regulatory requirement, we plan to revise SOP #4 and SOP #5 to specifically include consideration for vulnerable subjects with an impaired ability to give consent.

\* \* \*

I hope this response adequately addresses the inspectional observations and conveys to you the importance we place on compliance with the applicable regulatory requirements governing the IRB and informed consent. Please contact me at [REDACTED] if you need additional information or have any questions.

Sincerely,

[REDACTED]