

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
<small>DISTRICT ADDRESS AND PHONE NUMBER</small> 250 Marquette Ave, Ste. 600 Minneapolis, MN 55401 (612) 334-4100 Fax: (612) 334-4134		<small>DATE(S) OF INSPECTION</small> 4/9/2019-4/23/2019* <small>FEI NUMBER</small> 3015213291	
<small>NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED</small> <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> Sponsor-Investigator			
<small>FIRM NAME</small> <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> Sponsor-Investigator		<small>STREET ADDRESS</small> Hennepin County Medical Center, Dept Of Emergency Medicine, 701 Park Ave	
<small>CITY, STATE, ZIP CODE, COUNTRY</small> Minneapolis, MN 55415-1623		<small>TYPE ESTABLISHMENT INSPECTED</small> sponsor-investigator	
<p>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.</p>			
<p>DURING AN INSPECTION OF YOUR FIRM I OBSERVED: OBSERVATION 1 The sponsor failed to submit an IND to the FDA prior to conducting a clinical investigation with an investigational new drug.</p> <p>Specifically, study <div style="background-color: black; width: 100px; height: 1.2em; display: inline-block;"></div> and <div style="background-color: black; width: 100px; height: 1.2em; display: inline-block;"></div> were conducted without submitting INDs.</p>			
<p>OBSERVATION 2 Legally effective informed consent was not obtained from a subject or the subject's legally authorized representative, and the situation did not meet the criteria in 21 CFR 50.23 - 50.24 for exception.</p> <p>Specifically, subjects were enrolled and treated on the following studies without obtaining informed consent, with neither study appearing to meet the criteria for exception from informed consent:</p> <p>A. <div style="background-color: black; width: 100px; height: 1.2em; display: inline-block;"></div> - 747 subjects; and,</p> <p>B. <div style="background-color: black; width: 100px; height: 1.2em; display: inline-block;"></div> - at least 874 subjects.</p>			
<p>OBSERVATION 3 Not all changes in research activity were approved by an Institutional Review Board prior to implementation.</p> <p>Specifically,</p>			
SEE REVERSE OF THIS PAGE		<small>EMPLOYEE(S) SIGNATURE</small> Sharon L Matson, Investigator <div style="text-align: right; margin-top: 20px;"> <small>Sharon L. Matson Investigator Signed By: Sharon L. Matson-S Date Signed: 04-23-2019 13:11:52</small> <div style="border-top: 1px solid black; width: 20px; margin-left: 0;"></div> </div>	
		<small>DATE ISSUED</small> 4/23/2019	

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 4/9/2019-4/23/2019* FBI NUMBER 3015213291																					
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> Sponsor-Investigator																							
FIRM NAME <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> Sponsor-Investigator		STREET ADDRESS Hennepin County Medical Center, Dept Of Emergency Medicine, 701 Park Ave																					
CITY, STATE, ZIP CODE, COUNTRY Minneapolis, MN 55415-1623		TYPE ESTABLISHMENT INSPECTED sponsor-investigator																					
<p>A. For study <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div></p> <p>1. Serious adverse events (SAEs) were not reported to the IRB as required by the IRB, e.g.:</p> <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left; width: 15%;"><u>Subject#</u></th> <th style="text-align: left;"><u>SAE</u></th> </tr> </thead> <tbody> <tr><td>6</td><td>airway complication, required intubation</td></tr> <tr><td>26</td><td>hypoxia, required nasal cannula oxygen</td></tr> <tr><td>37</td><td>hypoxia, required nasal cannula oxygen, nasal/oral airway, and jaw thrust</td></tr> <tr><td>300</td><td>hypoxia, required nasal cannula oxygen, face mask oxygen, and nasal/oral airway</td></tr> <tr><td>346</td><td>hypoxia, required nasal cannula oxygen</td></tr> <tr><td>498</td><td>airway complication, required intubation</td></tr> <tr><td>594</td><td>pupils became pinpoint</td></tr> <tr><td>619</td><td>hypoxia, required intubation</td></tr> <tr><td>621</td><td>dystonia.</td></tr> </tbody> </table> <p>2. An additional treatment regimen was added to the study, using treatment Haloperidol at 10 mg from 9/21/2017 to 10/12/2017, without IRB review or approval.</p>				<u>Subject#</u>	<u>SAE</u>	6	airway complication, required intubation	26	hypoxia, required nasal cannula oxygen	37	hypoxia, required nasal cannula oxygen, nasal/oral airway, and jaw thrust	300	hypoxia, required nasal cannula oxygen, face mask oxygen, and nasal/oral airway	346	hypoxia, required nasal cannula oxygen	498	airway complication, required intubation	594	pupils became pinpoint	619	hypoxia, required intubation	621	dystonia.
<u>Subject#</u>	<u>SAE</u>																						
6	airway complication, required intubation																						
26	hypoxia, required nasal cannula oxygen																						
37	hypoxia, required nasal cannula oxygen, nasal/oral airway, and jaw thrust																						
300	hypoxia, required nasal cannula oxygen, face mask oxygen, and nasal/oral airway																						
346	hypoxia, required nasal cannula oxygen																						
498	airway complication, required intubation																						
594	pupils became pinpoint																						
619	hypoxia, required intubation																						
621	dystonia.																						
SEE REVERSE OF THIS PAGE		<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 60%; padding: 5px;"> EMPLOYEE(S) SIGNATURE Sharon L Matson, Investigator </td> <td style="width: 40%; padding: 5px; vertical-align: bottom;"> <div style="text-align: right;"> DATE ISSUED 4/23/2019 </div> <div style="text-align: right; font-size: 0.8em;"> Sharon L Matson Investigator Signed On: Sharon L Matson -S Date Signed: 04-23-2019 13:11:59 </div> </td> </tr> </table>		EMPLOYEE(S) SIGNATURE Sharon L Matson, Investigator	<div style="text-align: right;"> DATE ISSUED 4/23/2019 </div> <div style="text-align: right; font-size: 0.8em;"> Sharon L Matson Investigator Signed On: Sharon L Matson -S Date Signed: 04-23-2019 13:11:59 </div>																		
EMPLOYEE(S) SIGNATURE Sharon L Matson, Investigator	<div style="text-align: right;"> DATE ISSUED 4/23/2019 </div> <div style="text-align: right; font-size: 0.8em;"> Sharon L Matson Investigator Signed On: Sharon L Matson -S Date Signed: 04-23-2019 13:11:59 </div>																						
FORM FDA 483 (09/08)		PREVIOUS EDITION OBSOLETE																					
INSPECTIONAL OBSERVATIONS		PAGE 2 of 7 PAGES																					

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 4/9/2019-4/23/2019* FEI NUMBER 3015213291																			
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED [REDACTED] Sponsor-Investigator																					
FIRM NAME [REDACTED] Sponsor-Investigator		STREET ADDRESS Hennepin County Medical Center, Dept Of Emergency Medicine, 701 Park Ave																			
CITY, STATE, ZIP CODE, COUNTRY Minneapolis, MN 55415-1623		TYPE ESTABLISHMENT INSPECTED sponsor-investigator																			
<p>3. Seven-hundred and forty-seven (747) subjects in total were enrolled and treated on study a) over the 500 approved by the IRB, and b) over the 737 reported as the total enrollment to the IRB.</p> <p>4. An IRB-required annual progress report was not submitted until about 6/29/2018, past the 5/22/2018 expiration of approval.</p> <p>B. For study [REDACTED]</p> <p>1. Serious adverse events (SAEs) were not reported to the IRB as required by the IRB, e.g.:</p> <table border="0" style="width: 100%;"> <thead> <tr> <th style="text-align: left; padding-right: 20px;"><u>Subject#</u></th> <th style="text-align: left;"><u>SAE</u></th> </tr> </thead> <tbody> <tr><td>35</td><td>akathisia</td></tr> <tr><td>56</td><td>hypoxia, required nasal cannula oxygen</td></tr> <tr><td>74</td><td>airway complication, required intubation</td></tr> <tr><td>105</td><td>hypoxia</td></tr> <tr><td>134</td><td>hypoxia</td></tr> <tr><td>157</td><td>hypoxia</td></tr> <tr><td>192</td><td>hypotension</td></tr> <tr><td>197</td><td>hypoxia, required intubation.</td></tr> </tbody> </table> <p>2. A study change was submitted to the IRB and approved to voluntarily suspend study activities effective 7/16/2018, with a subsequent change submitted 11/5/2018 stating the study was closed. However, it appears the study continued with the same treatment regimen and data collection activities</p>				<u>Subject#</u>	<u>SAE</u>	35	akathisia	56	hypoxia, required nasal cannula oxygen	74	airway complication, required intubation	105	hypoxia	134	hypoxia	157	hypoxia	192	hypotension	197	hypoxia, required intubation.
<u>Subject#</u>	<u>SAE</u>																				
35	akathisia																				
56	hypoxia, required nasal cannula oxygen																				
74	airway complication, required intubation																				
105	hypoxia																				
134	hypoxia																				
157	hypoxia																				
192	hypotension																				
197	hypoxia, required intubation.																				
SEE REVERSE OF THIS PAGE		EMPLOYEE(S) SIGNATURE Sharon L Matson, Investigator <div style="text-align: right; font-size: small;"> Sharon L Matson Investigator Signed By: Sharon L. Matson-S Date Signed: 04/23/2019 13:11:59 X </div>																			
FORM FDA 483 (09/08)		PREVIOUS EDITION OBSOLETE																			
INSPECTIONAL OBSERVATIONS		DATE ISSUED 4/23/2019																			
PAGE 3 of 7 PAGES																					

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
<small>DISTRICT ADDRESS AND PHONE NUMBER</small> 250 Marquette Ave, Ste. 600 Minneapolis, MN 55401 (612) 334-4100 Fax: (612) 334-4134		<small>DATE(S) OF INSPECTION</small> 4/9/2019-4/23/2019* <small>FBI NUMBER</small> 3015213291	
<small>NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED</small> <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> Sponsor-Investigator			
<small>FIRM NAME</small> <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> Sponsor-Investigator		<small>STREET ADDRESS</small> Hennepin County Medical Center, Dept Of Emergency Medicine, 701 Park Ave	
<small>CITY, STATE, ZIP CODE, COUNTRY</small> Minneapolis, MN 55415-1623		<small>TYPE ESTABLISHMENT INSPECTED</small> sponsor-investigator	
<p>until at least the most recent enrollment of Subject 874 on 11/19/2018; and, the status of the study is posted on clinicaltrials.gov as "Recruiting". Changes in the study that do not appear to have been approved by the IRB include:</p> <ul style="list-style-type: none"> a) Continuing the study after the 7/16/2018 voluntary suspension submitted and approved; b) Discontinuing provision of a Notification of Enrollment to subjects on about 7/16/2018; and, c) Enrolling at least 874 subjects in total, over the 800 originally approved by the IRB. <p>3. An additional AMSS Data Validation sub-study was conducted without IRB review or approval.</p>			
<p>OBSERVATION 4</p> <p>An investigation was not conducted in accordance with the investigational plan.</p> <p>Specifically, not all study conduct was in accordance with the study plans submitted to and approved by the IRB for <div style="background-color: black; width: 100px; height: 1.2em; display: inline-block;"></div> and <div style="background-color: black; width: 100px; height: 1.2em; display: inline-block;"></div>, e.g.:</p> <p>A. There is no documentation to show all subjects were provided a Notification of Enrollment form, e.g.:</p> <ul style="list-style-type: none"> 1. <div style="background-color: black; width: 100px; height: 1.2em; display: inline-block;"></div> subject 1, 7, 9, 14, 15, 23, 46, 48, 161, 179, 197, 205, 299, 326, 332, 464, 511, 587, 593, 594, 607, 613, 631, and 633; and, 2. <div style="background-color: black; width: 100px; height: 1.2em; display: inline-block;"></div> subject 8, 9, 10, 66, 72, 136, 171, 172, 197, 205, 206, 208, 209, 213, 214, 215, 216, 217, and 874. <p>B. There is no documentation to show all Research Volunteers (RVs) that conducted study operations were trained, e.g.:</p> <ul style="list-style-type: none"> 1. <div style="background-color: black; width: 100px; height: 1.2em; display: inline-block;"></div> <p>RV <u>conducted study operations with</u></p> <p>ND 5, 8, 14, 173, 339, 343, 344</p>			
SEE REVERSE OF THIS PAGE		<small>EMPLOYEE(S) SIGNATURE</small> Sharon L Matson, Investigator <div style="text-align: right;"> <small>Sharon L. Matson Investigator Signed By: Sharon L. Matson-S Date Signed: 04-23-2019 13:11:59</small> X </div>	
<small>FORM FDA 483 (09/08)</small>		<small>PREVIOUS EDITION OBSOLETE</small>	
		INSPECTIONAL OBSERVATIONS	
		<small>PAGE 4 of 7 PAGES</small>	

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
<small>DISTRICT ADDRESS AND PHONE NUMBER</small> 250 Marquette Ave, Ste. 600 Minneapolis, MN 55401 (612) 334-4100 Fax: (612) 334-4134		<small>DATE(S) OF INSPECTION</small> 4/9/2019-4/23/2019* <small>FEI NUMBER</small> 3015213291	
<small>NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED</small> <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> Sponsor-Investigator			
<small>FIRM NAME</small> <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> Sponsor-Investigator		<small>STREET ADDRESS</small> Hennepin County Medical Center, Dept Of Emergency Medicine, 701 Park Ave	
<small>CITY, STATE, ZIP CODE, COUNTRY</small> Minneapolis, MN 55415-1623		<small>TYPE ESTABLISHMENT INSPECTED</small> sponsor-investigator	
MJ	304, 463, 502		
ML	184, 189, 325, 490		
HT	47; and,		
2.	<div style="background-color: black; width: 100px; height: 1.2em; display: inline-block;"></div>		
<u>RV</u>	<u>conducted study operations with</u>		
PD	175		
HL	35		
AK	40, 72		
LD	178, 179, 184		
EY	187, 190, 197.		
OBSERVATION 5 Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent. Specifically, for study <div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> and <div style="background-color: black; width: 100px; height: 1.2em; display: inline-block;"></div> there is no identification in source records to show who conducted: A. screening, and completion of Screening Sheets for either study; B. data collection from EMR, and completion of Chart Review form for either study; and, C. data validation, and completion of the AMSS Data Validation form for study <div style="background-color: black; width: 100px; height: 1.2em; display: inline-block;"></div>			
OBSERVATION 6			
SEE REVERSE OF THIS PAGE	<small>EMPLOYEE(S) SIGNATURE</small> Sharon L Matson, Investigator		<small>DATE ISSUED</small> 4/23/2019 <div style="font-size: 0.8em;"> Sharon L Matson Investigator Signed By: Sharon L Matson - S Date Signed: 04-23-2019 13:17:59 </div> <div style="text-align: center; margin-top: 5px;">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 4/9/2019-4/23/2019*	
		FEI NUMBER 3015213291	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED [REDACTED] Sponsor-Investigator			
FIRM NAME [REDACTED] Sponsor-Investigator		STREET ADDRESS Hennepin County Medical Center, Dept Of Emergency Medicine, 701 Park Ave	
CITY, STATE, ZIP CODE, COUNTRY Minneapolis, MN 55415-1623		TYPE ESTABLISHMENT INSPECTED sponsor-investigator	
<p>Failure to ensure proper monitoring of the study.</p> <p>Specifically, there is no documentation to show any monitoring of study [REDACTED] or [REDACTED]</p>			
<p>OBSERVATION 7</p> <p>Investigational drug disposition records are not adequate with respect to dates, quantity and use by subjects.</p> <p>Specifically, no clinical investigator-required investigational drug disposition records were maintained for either study [REDACTED] or [REDACTED]</p>			
<p>OBSERVATION 8</p> <p>Lack of records covering receipt and disposition of an investigational drug.</p>			
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Sharon L Matson, Investigator		DATE ISSUED 4/23/2019
	<div style="border: 1px solid black; padding: 2px;"> Sharon L Matson Investigator Signed By: Sharon L. Matson-S Date Signed: 04-23-2019 12:11:59 </div>		
FORM FDA 483 (09/08)		PREVIOUS EDITION OBSOLETE	INSPECTIONAL OBSERVATIONS
PAGE 6 of 7 PAGES			

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 4/9/2019-4/23/2019*	
		FEI NUMBER 3015213291	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED [REDACTED] Sponsor-Investigator			
FIRM NAME [REDACTED] Sponsor-Investigator		STREET ADDRESS Hennepin County Medical Center, Dept Of Emergency Medicine, 701 Park Ave	
CITY, STATE, ZIP CODE, COUNTRY Minneapolis, MN 55415-1623		TYPE ESTABLISHMENT INSPECTED sponsor-investigator	
Specifically, no sponsor-required investigational drug records were maintained for either study [REDACTED] [REDACTED] or [REDACTED]			
*DATES OF INSPECTION 4/09/2019(Tue), 4/10/2019(Wed), 4/11/2019(Thu), 4/15/2019(Mon), 4/16/2019(Tue), 4/17/2019(Wed), 4/18/2019(Thu), 4/23/2019(Tue)			
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Sharon L Matson, Investigator		DATE ISSUED 4/23/2019
	Sharon L Matson Investigator Signed By: Sharon L Matson -S Date Signed: 04-23-2019 13:11:59 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."



May 14, 2019





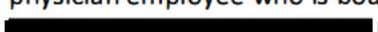
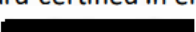
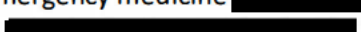

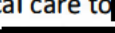
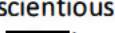
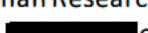
Michael Dutcher, Director
U.S. Food and Drug Administration
Minneapolis District Office
250 Marquette Avenue, Suite 600
Minneapolis, MN 55401


via email and US mail

 **Re: Response to Inspectional Observations; FEI Number 3015213291**

Dear Director Dutcher:

Between April 9 and April 23, 2019, FDA Investigator Sharon L. Matson performed an inspection of  conduct of two clinical research studies  (collectively referred to as the proportion of individuals adequately sedated (PIAS) after administration of available and standard of care drug products studies) at Hennepin Healthcare System Inc. ("Hennepin Healthcare"). Upon completion of the inspection, Ms. Matson issued a Form FDA 483, with eight inspectional observations listed.

I am responding to the Form FDA 483 with   Hennepin Healthcare  is a physician employee who is board-certified in emergency medicine     is a well respected doctor who is committed to providing high-quality medical care to  patients and to conducting important research in the emergency setting  is conscientious about meeting all regulatory requirements and Good Clinical Practice standards  is current on all of our Hennepin Healthcare's human subjects protection training requirements, including CITI training courses in Good Clinical Practice and ICH (14 modules), Primary Basic Course (10 modules), and Conflict of Interest (3 modules), as well as the as well as the CITI training in Good Clinical Practice and Human Research Protections for Biomedical Study Teams required by the University of Minnesota  recently completed the on site, in-person comprehensive training tailored to the needs of the Hennepin Healthcare research community, by experts in human subjects protection, law, and biomedical ethics.

As I hope this response demonstrates, everyone at Hennepin Healthcare, including , recognizes and understands the importance of complying with applicable human subjects protections, clinical trial-related regulatory requirements and Good Clinical Practice generally, which safeguard both clinical trial subjects and data integrity. We take our responsibilities to protect individuals enrolled in research very seriously. Our physicians are outstanding professionals and are required to receive extensive training in the law and ethics surrounding

human subjects research before they can become investigators in our institution, and on a continuing basis. We are committed to taking all action, where appropriate, to enhance those aspects of compliance raised by the inspectional observations. In addition to our response to the observations listed on the Form FDA 483, we have included our plans to take appropriate corrective actions.

Due to the complexity of the issues identified in the Form FDA 483 and what we think may be some confusion about the PIAS studies [REDACTED] conducted, before addressing each observation, we provide some critical background information.

Background

At the outset, it is important to be clear that in our view, and as explained in more detail below, no patients' rights, safety, or welfare were violated due to their enrollment in the PIAS studies. There were no subject deaths related to the study interventions, and there were no deaths in the cohort unrelated to study interventions. Additionally, there were no adverse events related to the actual study interventions, and all subjects were treated by attending emergency medicine physicians who work in the Emergency Department (ED) in accord with standard treatments used in the ED for sedation and standard medical practice. To be clear, the only research-related interventions in the PIAS studies were:

- 1) the **use of a stopwatch** to accurately measure time from administration of a sedative to adequate patient sedation,
- 2) the **use of an agitation assessment scale** (called the Altered Mental Status Scale (AMSS)) at specified time intervals, and
- 3) **data collection forms.**

Contrary to FDA's assertions in the Form FDA 483, the drug products (Olanzapine, Ziprasidone, Haloperidol, and Midazolam) administered to persons who presented in the ED with acute undifferentiated agitation were not study-related interventions. Instead, they are the exact treatments that are the standard of care in the ED setting used routinely by the physicians in the ED on a daily basis, and all persons treated in Hennepin Healthcare's ED would have received these exact same products to treat their acute undifferentiated agitation whether they were enrolled in the research or not. These drug products were administered to all patients according to the clinical judgment of the emergency medicine physicians, which was wholly unrelated to the study itself. At no time did any patient receive drug therapy for the sake of the research. We note that the ED has its own Treatment Protocols that operate at the direction of the ED department and represent their current thinking about standard of care treatments. They operate independently from any research studies. Although the ED Treatment Protocols suggested the use of one drug for a certain period of time as initial preferential treatment, at all times the emergency medicine physicians could choose to use a different drug based on their clinical judgment and not enroll any given subject.

To reiterate, all patients who received drug therapy met the criteria for sedation due to their acute undifferentiated agitation in the ED at the discretion of the treating clinician. Acute undifferentiated agitation in itself is a potentially life-threatening process, and the ED providers

take great care in diligently treating this illness. Treating acute undifferentiated agitation in the ED is taken very seriously by our providers because of its significant potential for patient injury and complications, as well as provider injury. The determination to sedate a patient was based on the clinical judgment of the emergency medicine physicians and thus the determination to sedate a patient was independent from whether they were enrolled in the PIAS studies. Therefore, all patients received the same medical therapy and care that they would have received whether enrolled in these studies or not. So, the actual study-related interventions do not include the administration of the drug products themselves. The three study interventions listed above undeniably do not “significantly increase the risks (or decrease the acceptability of the risks) associated with the use of the drug product(s)” at issue.¹

We also note that all Hennepin Healthcare ED personnel who were involved with the PIAS studies were board-certified or board-eligible emergency medical physicians, and any resident physicians involved in the study were directly supervised by the attending staff. Furthermore, all study coordinators and research volunteers (RVs) were trained in proper clinical trial data collection procedures and specifically for proper data collection for the PIAS studies, including use of the AMSS. Also relevant to these studies, the emergency medicine physicians were authorized to prescribe and administer these drug products to patients and were specifically trained in all aspects of emergency care that might be necessary. Finally, all patients who presented with acute undifferentiated agitation were treated in the ED’s 16-bed Special Care Unit which had numerous heightened features of emergency care such as a dedicated emergency medicine physician, 2 assigned nurses at all times along with a health care assistant, and was equipped with all necessary monitoring and emergency equipment.

We also think it is paramount to clarify the various operations of the ED related to their quality improvement and quality assurance activities. The goal of these activities is to engage in holistic initiatives with the intent of improving clinical practice for patients, the majority of whom come from underserved populations. To this end, the ED routinely scrutinizes its health care delivery practices and internal procedures by systematically collecting data on these practices for internal use. To do this they often standardize various components of care, such as the development of an ED Treatment Protocol which outlines first line therapy for a particular condition for predetermined lengths of time. In fact, before [REDACTED] studies, the ED had put in place ED Treatment Protocols for the four drug products used to treat acute undifferentiated agitation. Of particular note, in [REDACTED] studies the first line treatment was not dictated by [REDACTED] study protocols, but instead the preferential use of the drugs was driven by the ED Treatment Protocols already in place. And when [REDACTED] was voluntarily paused on July 16, 2018, the emergency medicine physicians continued to use the first line treatments as dictated by the ED Treatment Protocols. Similarly, when the research was paused, the ED resumed its routine collection of similar information as part of their quality improvement and quality assurance activities.

Similarly, the overall purpose of [REDACTED] studies was to contribute to evidence-based medicine. The specific purpose was to measure the proportion of individuals adequately sedated after administration of the available and standard of care drug products. These drug

¹ See 21 CFR 312.2(b)(iii).

products administered in the ED were all FDA-approved, were essentially used in accord with their labeling, were used within FDA's long-standing policy regarding the practice of medicine, and were considered the standard of care. The study was not intended to be reported to FDA as a well-controlled study in support of a new indication for use or to support any other significant changes in labeling, and otherwise met the investigational new drug (IND) application exemption criteria in FDA's regulations at 21 CFR 312.2(b).

We acknowledge that some study-related documents, including the protocols for the PIAS studies, were not drafted as precisely as would have been ideal. For example, the protocols do not clearly distinguish the actual study-related interventions from the standard therapies provided in the ED that subjects would have received whether or not they were enrolled in the studies. This imprecise drafting could be the source of some of the FDA inspector's misperception about the sedation drugs used in the ED in relation to the PIAS studies. Similarly, in various study-related documents, [REDACTED] mistakenly described the PIAS studies as a quality improvement project that was an observation of clinical practice, and suggested that the studies were not clinical research.

However, these drafting problems and confusion about the nature of this research do not change the fact that the drugs were not study-related interventions. Of utmost importance, the provision of the drug therapies used was not driven by [REDACTED] research protocols; instead, the treating emergency medicine physicians directed the use of these drug therapies based on their clinical judgment regarding the medical condition of their patients and the ED Treatment Protocols. [REDACTED] PIAS studies are pragmatic research conducted in a real-world setting that relate to standard clinical therapies, but those therapies are not research interventions. Under no circumstances could [REDACTED] PIAS studies be considered adequate and well-controlled trials designed to evaluate the safety and effectiveness of the drug products, and they certainly were not intended to affect any regulatory decision making.

Observation # 1:

The sponsor failed to submit an IND to the FDA prior to conducting a clinical investigation with an investigational new drug.

Specifically, studies [REDACTED] were conducted without submitting INDs.

Response to Observation # 1:

We strongly disagree with Observation 1 for two separate reasons: 1) the drugs at issue were not interventions in [REDACTED] studies and therefore no investigational drug products were being evaluated and 21 CFR 312 is not applicable; and 2) even if one were to accept the assertion that the drug products were research interventions, the criteria for an exemption from needing an IND at 21 CFR 312.2(b) were clearly met.

1) An IND Was Not Needed Because the Drugs Were Not Research Interventions

As explained in the background discussion above, the three study-related interventions (the use of a stopwatch, an agitation scale, and data collection forms) were the only departures from routine clinical care when patients with acute undifferentiated agitation were in the ED.

The administration of the drug products should not be considered a research intervention for several reasons. First, the study protocols did not dictate which drugs were used for an individual patient. The emergency medicine physicians involved in the study used their medical judgment and discretion to determine the proper medical care of the individuals they encountered, including which drug products, if any, to administer for the treatment of agitation. At no time was any patient sedated for their agitation for the sake of enrolling them in the research. Moreover, use of all four drug products at issue for acute undifferentiated agitation were part of the standard of care used by Hennepin Healthcare for sedation treatment in the ED and used as standards of care around the world. See Appendix 2.

Although [REDACTED] study protocols described changes in preferential initial treatment in varied time intervals for acute undifferentiated agitation based on the ED Treatment Protocols, this change does not mean the drug products are research-related interventions. At all times during the study, the emergency medicine physicians were free to use whichever therapy they thought was most appropriate using their professional medical judgment and could choose not to enroll any particular subject. It is worth noting that at all times during the conduct of the PIAS studies all drug products used in the Hennepin Healthcare ED as the standard of care for sedation were available for physicians to choose to use for any particular patient.

2) Even if 21 CFR Part 312 Was Applicable, the Exemption Criteria Were Met

We disagree with Observation 1 that [REDACTED] failed to submit an IND to FDA prior to conducting a clinical investigation with an investigational new drug, and that the IND exemption criteria appear to not have been met. First, the products at issue should not be considered investigational new drugs. Each drug product is FDA-approved, and each was essentially used in accordance with its approved labeling. Further, the use of each drug fell within the practice of medicine and the standard of care for sedation in the ED.

Even if the IND regulations were applicable to the PIAS studies, the use of these drug products meet the IND exemption criteria set forth at 21 CFR 312.2(b). FDA's regulations describe the five criteria that must be met for a clinical investigation of a marketed drug to be exempt from the IND requirements.

Under 21 CFR 312.2(b)(1), a clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of Part 312 when the following criteria are met:

- 1) **21 CFR 312.2(b)(1)(i)** states that the investigation cannot be intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.

This criterion is clearly met. With these investigator-initiated trials, ██████ had no intention whatsoever to submit the data to FDA in support of a new indication for use nor to support any other significant changes in the labeling of these drugs. Rather, ██████ was attempting to contribute to evidence-based medicine by accurately recording the time to sedation with each of these four drugs in the ED setting. Furthermore, the PIAS studies were not designed or powered to meet FDA's regulatory requirements for data that would support changes to drug labeling.²

- 2) **21 CFR 312.2(b)(1)(ii)** states that if the drug that is undergoing investigation is lawfully marketed as prescription drug product, the investigation cannot be intended to support a significant change in the advertising for the product.

This criterion is met. It is undisputed that all four drugs, Olanzapine, Ziprasidone, Midazolam, and Haloperidol, are all FDA-approved and lawfully marketed. Further, ██████ had no intention to use the studies to support a change in advertising for the products. Rather, these trials were intended to inform clinical practice.

- 3) **21 CFR 312.2(b)(1)(iii)** states that the investigation cannot involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug products.

This criterion is also clearly met. In this instance, although the drugs were not study related interventions, the investigators and the Institutional Review Board (IRB) opined that the use of the drugs for sedation in the ED was essentially in accord with their approved labeling, and that their use did not significantly increase the risk or decrease the acceptability of the risks to subjects. Similarly, all four drug products were considered to be the standard of care when encountering patients with acute undifferentiated agitation in the ED. Thus, Hennepin Healthcare's ED had determined that the risks associated with administering these drugs to agitated patients in the ED were acceptable (and were not significantly increased). Furthermore, these drugs were administered by emergency medicine physicians who were trained to properly evaluate their patients' medical conditions, to make professional judgments about the appropriate use of various medical therapies, to treat any related side effects, and to appropriately monitor their patients post-drug administration.

- a) Specifically, Haloperidol is indicated for schizophrenia and control of ticks and vocal utterances associated with Tourette's disorder.³ It is used in EDs as a treatment routinely for persons with agitation from these and other conditions. It does

² Of note, the PIAS studies were investigator-initiated trials that were not funded by the federal government nor did they have any pharmaceutical company funding or support. Rather they were internally funded by Hennepin Healthcare.

³ See, e.g., Haloperidol Lactate Injection Prescribing Information, <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8397a841-f240-4767-9dcd-781e6d3f7c7f>.

contain a black box warning regarding increased mortality in elderly patients with dementia related psychosis and it can cause, among others, cardiac-related side effects. However, Haloperidol is an old drug with a well-known safety profile from extensive post-market use, and the use in patient care by Hennepin Healthcare's emergency medicine physicians is generally consistent with the indications and risk profile.

- b) Next, Ziprasidone is indicated for acute manic or mixed episodes associated with bipolar disorder and acute agitation in schizophrenia.⁴ It has a black box warning regarding an increased mortality associated with use in elderly patients with dementia related psychosis. Other warnings describe potential cardiac issues. Ziprasidone is routinely used as a sedative in various hospital and ED settings for psychiatric illnesses. Its use by Hennepin Healthcare's emergency medicine physicians, again, is generally consistent with the labeled indications and risk profile.
- c) Olanzapine is indicated for the treatment of acute agitation associated with schizophrenia and bipolar mania.⁵ It has a black box warning regarding an increased mortality associated with use in elderly patients with dementia related psychosis. It also contains warnings about neuroleptic syndrome. Olanzapine commonly is used for sedation in the ED and other hospital settings and its use by Hennepin Healthcare's emergency medicine physicians is consistent with the labeling and the product's risk profile.
- d) Last, Midazolam is labeled for use in sedation and induction of anesthesia.⁶ Its labeling contains a boxed warning stating that its use can be associated with respiratory depression and respiratory arrest. Thus, the label recommends continuous monitoring of patients post administration of the drug. Midazolam is routinely used as a sedative in various hospital and ED settings. The use by the emergency medicine physicians is consistent with the indications, risk profile, and available safety monitoring.

The use of these products is generally consistent with their approved labeling and the Hennepin Healthcare emergency medicine physicians are skilled professionals who are rigorously trained and experienced in maintaining a patient's airway, supporting ventilation, and continuously monitoring patients who have received these drugs. We also point to a comprehensive list of references that show throughout the U.S. and throughout the world these drugs are used in this specific population of patients

4 See, e.g., Geodon (ziprasidone mesylate injection) Prescribing Information, <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8326928a-2cb6-4f7f-9712-03a425a14c37>.

5 See, e.g., Olanzapine Injection Prescribing Information, <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1e9666ef-4271-4834-8496-ccb3125d83db>.

6 See, e.g., Midazolam Hydrochloride Injection Prescribing Information, <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=737361a0-8db1-4d3c-ba5e-44df3f49fa22>.

routinely. See Appendix 2. For all the reasons articulated above, we do not believe that using these drugs to treat patients with acute undifferentiated agitation in the ED constitutes a significantly increased risk or a decrease in the acceptability of the risks associated with the use of these drugs.

- 4) **21 CFR 312.2(b)(1)(iv)** states that the investigation must be conducted in compliance with the requirements for institutional review set forth in Part 56 and with the requirements for informed consent in Part 50.

This criterion is also met. First, an appropriately constituted and properly registered IRB reviewed and approved the protocols under appropriate review procedures. Next, the IRB did not require informed consent from the participants because it determined that a waiver of informed consent was appropriate under 45 CFR 46.116(d). While FDA's regulations do not currently contain a similar provision for waiver of informed consent, it is consistent with current FDA policy. FDA issued an enforcement discretion guidance in 2017⁷ describing its intention not to object to an IRB's waiving or altering of 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. FDA issued this guidance as an interim measure while it promulgates regulations that reflect the statutory authority granted to FDA by the 21st Century Cures Act, which explicitly permits an exception from the informed consent requirements for such clinical trials.⁸ In the guidance, FDA states "until FDA promulgates these regulations we do not intend to object to an IRB approving a consent procedure that does not include or that alters some or all of the elements of informed consent set forth in 21 CFR 50.25 or waiving the requirements to obtain informed consent when the IRB finds and documents that" the four provisions in 45 CFR 46.116(d) listed above are met.⁹ In late 2018, FDA issued a Federal Register notice stating its intention to promulgate regulations that would allow for the waiver of informed consent when a clinical investigation poses no more than minimal risk to human subjects.¹⁰ As the PIAS studies both involved study interventions that are no more than

7 Food and Drug Administration, *Guidance for Sponsors, Investigators, and Institutional Review Boards – IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects* (July 2017), <https://www.fda.gov/media/106587/download>.

8 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>

9 Food and Drug Administration, *Guidance for Sponsors, Investigators, and Institutional Review Boards – IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects* at 4 (July 2017), <https://www.fda.gov/media/106587/download>.

10 83 FR 57378 (Nov. 15, 2018).

minimal risk (i.e. the use of a stopwatch an agitation scale, and data collection forms) and met the criteria for a waiver of informed consent, the IRB clearly acted appropriately in not requiring informed consent from the study participants.

- 5) In addition, Hennepin Healthcare's IRB further protected the subjects enrolled in these studies by requiring the investigators to provide them, when possible, pertinent information about the trials and their enrollment. And, in both studies subjects were given the opportunity to have their data removed from the research database if they chose. 21 CFR 312.2(b)(1)(v) states that the investigation must be conducted in compliance with the requirements of 21 CFR 312.7.

This requirement is also met. 21 CFR 312.7 prohibits preapproval promotion of investigational drug products. Under this regulation, an investigator cannot represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. In this instance, the drug products at issue were all FDA-approved, were not study related interventions, and were used within the practice of medicine and the standard of care. Furthermore, [REDACTED] did not engage in any promotional activities nor represent that these drugs were safe or effective for an unapproved use.

Corrective Actions Related to Observation # 1:

The FDA inspector may have incorrectly concluded that an IND was necessary and/or that the IND exemption appeared to not have been met due to some imprecise language in the PIAS protocols. Therefore, we have taken the following corrective actions:

- 1) We have implemented the required use of a standardized protocol template for every submission of an investigator-initiated protocol to the IRB, and rejection by the IRB of all investigator-initiated submissions which do not follow the template and/or are otherwise incomplete. We believe that the use of the protocol template will help investigators be more accurate and complete in the descriptions of their studies.
- 2) On May 7 and 8, 2019, an on-site, mandatory comprehensive retraining for all investigators was provided.¹¹ This training was designed to meet the specific needs and research interests of Hennepin Healthcare. The training addressed, among other topics, FDA regulatory requirements related to INDs, Investigational Device Exemptions (IDEs), Good Clinical Practice, research ethics, and clinical research including the use of investigational products. [REDACTED] completed the training session in-person.
- 3) Out of an abundance of caution, we are establishing a policy of mandatory pre-review which will be coordinated by Hennepin Healthcare's Office of Education and Quality in Clinical Research for all Full Committee IRB submissions that involve an investigator-initiated clinical research proposal, which will include an assessment of whether an IND or Investigational Device Exemption (IDE) may be needed prior to submission to the IRB.

¹¹ Investigators unable to attend in person will be required to view the recorded version and all investigators were provided access to the training materials.

Observation # 2:

Legally effective informed consent was not obtained from a subject or the subjects' legally authorized representative, and the situation did not meet the criteria in 21 CFR 50.23 - 50.24 for exception.

Specifically, subjects were enrolled and treated on the following studies without obtaining informed consent, with neither study appearing to meet the criteria for exception for informed consent: A. [REDACTED] 747 subjects; and, B. [REDACTED] at least 874 subjects.

Response to Observation # 2:

We do not agree that informed consent was required to be obtained from the subjects in the PIAS studies. Rather, the IRB's decision to waive informed consent under 45 CFR 46.116(d) in the PIAS studies was justified, and was in accord with FDA's current pronouncements on the applicability of the use of this waiver for FDA-regulated studies. Observation 2 mentions two exceptions from informed consent at 21 CFR 50.23 and 21 CFR 50.24 that are currently allowable for use under FDA's regulations and notes that those provisions are not applicable in this instance. However, Observation 2 does not appear to take into account FDA's current policies regarding the waiver of informed consent including its use of enforcement discretion and its statement of intent to promulgate regulations that adopt 45 CFR 46.116(d) into FDA's regulations. Thus, we contend that the requirement to obtain informed consent was properly waived by the IRB. Furthermore, as described below, the IRB appropriately determined that the waiver of informed consent criteria in 45 CFR 46.116(d) were met.

Waiver of Informed Consent Was Appropriate

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.

We address each of these in turn:

- a) **The Research Involves No More than Minimal Risk:** The waiver of the informed consent requirements at 45 CFR 46.116(d) is only applicable to studies that are considered to be minimal risk. Minimal risk studies are defined by regulation as those where "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".¹²

¹² See 21 CFR 50.3(k) and 45 CFR 46.102(j).

In these studies, the principal investigator [REDACTED] 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 scale to assess the individual's level of agitation; and, 3) the collection of various data points. 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 ER setting, involved no more than minimal risk. This is an appropriate interpretation of the regulations for several reasons described below.

First, the IRB regulations at 21 CFR 56.111(a)(2) state that for approval the "risks to subjects [must be] reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may 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)" In fact, the Department of Health and Human Services' (DHHS) Office of Human Research Protections (OHRP) issued a draft guidance document in 2014 on disclosing reasonably foreseeable risks in research evaluating standards of care.¹³ 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."¹⁴ OHRP clarified 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 PIAS 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 adequate sedation at 15 minutes. Hence, based on FDA's regulation and OHRP's guidance, the principal investigator and the IRB believed that the drugs themselves should not be considered study-related interventions. Therefore, the risks of these studies were 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) and not the drug products themselves.

- b) The waiver will not adversely affect the rights and welfare of the subjects:** During the conduct of these studies, the patients who presented to the ED with acute

13 Office of Human Research Protections, *Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care* (Mar. 2016), <https://www.hhs.gov/ohrp/regulations-and-policy/requests-for-comments/draft-guidance-disclosing-risk-in-standards-of-care/index.html>

14 *Id.*

undifferentiated agitation received the standard of care therapies for their medical condition. The drug treatments that the patients received (i.e. Haloperidol, Midazolam, Olanzapine, and Zipasidone) constitute the standard of care in ED settings and those medical standards were not deviated from in any way for the purposes of the research. And as previously mentioned, all emergency medicine physicians had the discretion to use any drug therapies they decided were appropriate at any time using their clinical judgment to make individual treatment decisions.

Further, based on the patient's medical condition when arriving at the ED (i.e. presenting with acute undifferentiated agitation), such patients would have been unable to consent to clinical care. In clinical scenarios such as this where there is an emergency and time to treatment is critical, obtaining consent is not an ethical requirement. Rather, it is most important to act in the patient's best interest and to provide appropriate care according to standard treatment protocols. Similarly, due to the nature of the patient's medical condition at the time of enrollment by the emergency medicine physicians, it would have been infeasible to obtain consent to participate in this minimal risk research.¹⁵ Thus, we do not believe that the rights and welfare of the subjects were adversely affected by the use of the waiver.

- c) **The research could not practicably be carried out without the waiver:** Because the participants had acute undifferentiated agitation, a condition that is a medical emergency, and needed urgent intervention in the form of medical sedation by emergency medicine physicians, they could not have provided legally effective informed consent to participate. Similarly, subjects' legally authorized representatives were not typically available to provide consent and/or the rapidity with which treatment must be administered precluded the ability to obtain informed consent.¹⁶ Therefore, the research could not practicably have been carried out without the waiver.
- d) **Whenever appropriate the subjects will be provided with additional pertinent information after participation:** The IRB specifically required that the subjects who were enrolled in the PIAS studies received notification of enrollment once they were no longer incapacitated and could make decisions themselves. At that time, the subjects were provided with additional pertinent information. And for both studies, subjects or their legally authorized representative were also given an opportunity to request their data be removed from the study database if they wished.

As explained above in response to Observation 1, while FDA's regulations do not currently contain a provision similar to 45 CFR 46.116(d) for waiver of informed consent, FDA has issued an enforcement discretion guidance¹⁷ describing its intention not to object to an IRB's waiving or

¹⁵ See generally M. Martel et al., *A Brief Assessment of Capacity to Consent Instrument in Acutely Intoxicated Emergency Department Patients*, 36 AM. J. OF EMER. MED. 18 (Jan. 2018).

¹⁶ [REDACTED]

¹⁷ Food and Drug Administration, *Guidance for Sponsors, Investigators, and Institutional Review Boards – IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No*

altering of 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.¹⁸ FDA also has issued a Federal Register Notice describing its intention to adopt a waiver of informed consent provision in line with 45 CFR 46.116(d).¹⁹

We also note that in an article published in 2015, FDA senior leadership and other thought leaders called for FDA to “establish a risk-based approach to obtaining informed consent in [pragmatic clinical trials] that would facilitate the conduct of [pragmatic clinical trials] without compromising the protection of enrolled individuals or the integrity of the resulting data.”²⁰ The authors, which included FDA officials, expressed concern “that current FDA requirements for obtaining individual informed consent may deter or delay the conduct of pragmatic clinical trials intended to develop reliable evidence of comparative safety and effectiveness of approved medical products that are regulated by the FDA.”²¹ The design and intent of these PIAS studies were consistent with these forward-thinking principles.

Last, as a point of clarification, Observation 2 notes that [REDACTED] had at least 874 subjects enrolled. This number is incorrect. This study was initiated on May 29, 2018 and was voluntarily paused by [REDACTED] on July 16, 2018. In the little over 6 weeks the study was actively enrolling subjects, there were only 206 subjects enrolled. As explained below in response to Observation 3.B.2, after the study was paused, the ED collected some similar-type information as part their routine quality improvement and quality assurance activities. We think the FDA inspector mistakenly considered that information to be a part of or related to [REDACTED] study.

Corrective Actions Related to Observation # 2:

As [REDACTED] and the IRB appropriately analyzed and applied the waiver of informed consent criteria, no corrective actions are planned with regard to Observation 2.

Observation # 3:

Not all changes in research activity were approved by an Institutional Review Board prior to implementation.

More Than Minimal Risk to Human Subjects (July 2017),

<https://www.fda.gov/media/106587/download>.

18 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”. Office for Human Research Protections, *Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care* (Mar. 2016),

<https://www.hhs.gov/ohrp/regulations-and-policy/requests-for-comments/draft-guidance-disclosing-risk-in-standards-of-care/index.html>

19 83 FR 57378 (Nov. 15, 2018).

20 ML Anderson et al., *The Food and Drug Administration and pragmatic clinical trials of marketed medical products*, 12 CLINICAL TRIALS 511 (2015).

21 *Id.*

Specifically,

A. For study [REDACTED]:

1. Serious Adverse Events (SAE) were not reported to the IRB as IRB (examples in 483 omitted here).
2. An additional treatment regimen was added to the study, using treatment Haloperidol at 10 mg from 9/21/2017 to 10/12/2017, without IRB review or approval.
3. Seven-hundred and forty-seven (747) subjects in total were enrolled and treated on study a) over the 500 approved by the IRB, and b) over the 737 reported as the total enrollment to the IRB.
4. An IRB required annual progress report was not submitted until about 6/29/2018, past the 5/22/2018 expiration of approval.

B. For study [REDACTED]:

1. Serious adverse events (SAEs) were not reported to the IRB as required by the IRB (examples in 483 omitted here)
2. A study change was submitted to the IRB and approved to voluntarily suspend study activities effective 7/16/2018, with a subsequent change submitted 11/5/2018 stating that the study was closed. However, it appears the study continued with the same treatment regimen and data collection activities until at least the most enrollment of Subject 874 on 11/19/2018; and, the status of the study is posted on clinicaltrials.gov as "Recruiting". Changes in the study that do not appear to have been approved by the IRB include:
 - a. Continuing the study after the 7/16/2018 voluntary suspension submitted and approved;
 - b. Discontinuing provision of a Notification of Enrollment to subjects on about 7/16/2018; and,
 - c. Enrolling at least 874 subjects in total, over the 800 originally approved by the IRB.
3. An additional AMSS Data Validation sub-study was conducted without IRB review or approval.

Response to Observation # 3:

We do not agree with Observations 3.A.1 and 3.B.1 as they are based on the false premise that the drug therapies provided to patients as part of standard of care by the emergency medicine physicians, were study related interventions. Observations 3.A.1 and 3.B.1 allege that SAE's were not reported as required by the IRB. However, there were no SAE's that occurred during the PIAS studies that were related to the actual study interventions (the use of the stopwatch,

the agitation scale, and the data collection). Therefore, all of the examples of alleged failures listed in Observation 3.A.1 and 3.B.1 were related to the drug products administered to patients as part of their clinical care and were not related to the study interventions, and therefore were misidentified as SAEs that were improperly documented and reported.

We acknowledge that in some communications to the IRB, [REDACTED] mistakenly attributed adverse events related to the drug products to [REDACTED] PIAS studies. This confusion arose because the protocol described and the data collection forms for the PIAS studies captured adverse event information related to the subject's medical care. The collection of these adverse events seemed appropriate at the time to collect in order to have a more fulsome picture of patient's experiences with the drug products to serve as descriptive information in any publications about the PIAS studies. In retrospect [REDACTED] should have been more clear in both [REDACTED] communications to the IRB, and in [REDACTED]²² about which outcomes were attributed to the study interventions and which were related to standard care (that patients would have received whether or not they were enrolled in the research). However, this imprecise drafting does not change the fact that the drugs were provided as part of standard therapy and were not research related interventions. Furthermore, we note that no subjects' rights, safety, and welfare were compromised by this confusion.

Observation 3.A.2 states that there was a change in the dose of Haloperidol that was not approved by the IRB. Observation 3.A.2 is based on the incorrect premise that the drug products that were administered clinically to patients as part of their standard care were study related interventions and the incorrect view that an IND was needed to conduct this study which would have made 21 CFR 312.66 applicable. While the protocols included information about the standard treatment regimens for these drug products, in retrospect, this information caused confusion about what aspects included in the protocol were research related interventions. However, this imprecise drafting does not change the fact that the drugs were provided as part of standard therapy and were not research related interventions. Furthermore, we note that no subjects' rights, safety, and welfare were compromised by this confusion.

Observation 3.A.3 notes that more subjects were enrolled in the study than were approved by the IRB to be enrolled. We acknowledge that [REDACTED] should have sought approval from the IRB to enroll more subjects than were allowed under the IRB's approval according to 21 CFR 312.66 and 21 CFR 56.108(a).

Observation 3.A.4 notes that the IRB's approval of the study lapsed for about a month's time because [REDACTED] submitted the continuing review form past the date of the expiration of IRB approval. We acknowledge that the study's approval lapsed during this time, mostly due to [REDACTED] having been [REDACTED] and we note that no subjects' rights, safety, and welfare were compromised by this short lapse in IRB approval. Of note, [REDACTED] submitted the continuing review to the IRB upon [REDACTED]

22 [REDACTED]

Observation 3.B.2 alleges that the study continued after a voluntary pause occurred on 7/16/18. We disagree that the study continued after it was voluntarily paused. [REDACTED] had informed the IRB via written communication dated 7/16/18 that [REDACTED] was stopping [REDACTED] study and no subjects were enrolled after that date. However, the ED, unrelated to [REDACTED] research, continued to collect similar-type information in accord with its routine quality improvement and quality assurance activities. Of note, the quality improvement and quality assurance information was not stored in research binders nor was it entered into the study's REDCap electronic database. We think the FDA inspector mistakenly identified this quality improvement information in her consideration of [REDACTED] study.

Thus, the allegations in 3.B.2.a), b), and c) are all incorrect.

- a) The research did not continue beyond 7/16/18.
- b) The Notice of Enrollment was intentionally not provided to patients who were not enrolled in research.
- c) And, as only 206 subjects were enrolled in the research before it was paused, the number of subjects did not exceed the amount initially approved by the IRB.

Last, Observation 3.B.2 also mentions that the status of [REDACTED] on clinicaltrials.gov was listed as "recruiting" past July 16, 2018. [REDACTED] posted the study on clinicaltrials.gov not because it met the criteria for the posting of an applicable clinical trial at 42 CFR 11.10(a) but because some journals, such as the Academic Emergency Medicine Journal, required the posting of the trial in a publicly available database as a prerequisite for publication.²³ We think this posting had the inadvertent consequence of suggesting to the FDA inspector that the drug products were research related interventions. We also acknowledge that the study's status should have been changed to "Active, not recruiting" as of July 16, 2018.

Observation 3.B.3 alleges that an additional AMSS Data Validation sub-study was conducted without IRB review or approval. We disagree with this observation. No additional study was conducted. We think the FDA inspector was instead confused by the fact that when two research volunteers were available, they would both use the AMSS on a single subject. Information describing this assessment was recorded on a separate study-related form labeled "AMSS Validation Data Form". The form was not identified as a sub-study, nor was it intended as a sub-study, but rather was to gather additional information to internally validate the agitation assessments being made.

Corrective Actions Related to Observation # 3:

- 1) To ensure that [REDACTED] and other investigators at Hennepin Healthcare do not conflate research related risks with the risks associated with the provision of standard of care therapies, we are requiring the use of a protocol template for IRB submissions for investigator-initiated research that requires a clear delineation between research

23 Academic Emergency Medicine Author Instructions (Apr. 13, 2018), http://www.saem.org/docs/default-source/aem-e-t/aem-e-t-author-instructions-4-13-2018-d1-sjr.pdf?sfvrsn=2afd35fd_2.

interventions and standard medical therapy. This protocol template will thus eliminate the confusion surrounding which adverse events are attributable to the study interventions and which are not.

- 2) To ensure that [REDACTED] and other investigators at Hennepin Healthcare are aware of and comply with various IRB related requirements (e.g. not letting IRB approval lapse and not enrolling more subjects than the IRB initially approved), we just required re-training on May 7 and 8, 2019 of all investigators on Hennepin Healthcare's IRB policies and the IRB requirements at 21 CFR Part 56.
- 3) Hennepin Healthcare and [REDACTED] agree that:
 - a. [REDACTED] will not serve as a sole principal investigator on any research for the next three years.
 - b. A Research Mentor will be assigned to supervise all of [REDACTED] research activities for three years. This supervision will include review of all protocols on which [REDACTED] serves as a co-principal or sub-investigator; and oversight of the conduct of the research.

Observation # 4:

An investigation was not conducted in accordance with the investigational plan.

Specifically, not all study conduct was in accordance with the study plans submitted to and approved by the IRB for [REDACTED] e.g.:

- A. There is no documentation to show all subjects were provided a Notification of Enrollment form, e.g.:
 1. [REDACTED] (list of subjects omitted)
 2. [REDACTED] (list of subjects omitted)
- B. There is no documentation to show that all Research Volunteers (RVs) that conducted study operations were trained, e.g.:
 1. [REDACTED] (list of RVs and subjects omitted)
 2. [REDACTED] (list of RVs and subjects omitted)

Response to Observation # 4:

In response to Observation 4.A, we assert that the study was generally conducted in accordance with the investigational plan. We do acknowledge, however, that the Data Collection case report forms used by the research staff to document receipt of the Notification of Enrollment form did not, in a small number of instances, indicate that a subject was given the Notification of Enrollment. We recognize this is a departure from the procedures required under the protocol and by the IRB, but in retrospect we realize that the form was poorly drafted. The data collection instrument simply recorded whether a subject received the form, but does not have a place to indicate why a subject might not have received the form for reasons beyond the control of the research volunteers. In some instances, a subject may have left the ED against medical advice, they may have refused discharge papers, and/or they may have eloped (i.e. left the ED

without letting ED staff know). In the future for other studies, we plan to clarify such forms to state something like, "Did the subject receive a Notification of Enrollment form? Y or N? If N, why not?" We expect that this change will more accurately document what actually happened in the ED with each subject.

In addition, for study [REDACTED] in Observation 4.A.1, we note that based on the FDA inspector's count of 24 forms which did not indicate that a subject received the Notification of Enrollment form, that amounts to only 3% of the total number of subjects enrolled. We strive to have complete and accurate record-keeping, and regret that the form was not designed to capture the reasons why a subject may not have received the form.

Last, the number of subjects listed by the FDA inspector in Observation 4.A.2 is incorrect. Only subjects 8, 9 10, 66, 72, 136, 171, 172, 197, and 217 were enrolled in [REDACTED]. The other numbers listed reflect patients whose information was included in the ED's quality improvement and quality assurance activities, and thus were not enrolled in research and should not have received the Notification of Enrollment form. As above, based on the FDA inspector's count of 10 subjects who did not receive the form, that amounts to less than 5% of subjects where the Data Collection form was incomplete. Again, we strive to have complete and accurate records and regret that the form was not designed to accurately record what may have occurred in the ED.

Observation 4.B does not seem to be related to conducting the study in accordance with the investigational plan. Observation 4.B suggests that there was no documentation that the RVs were appropriately trained. We disagree with Observation 4.B as all RVs received comprehensive training. Specifically, RVs undergo a competitive selection process and then must complete both general and specific research training before they can begin. The general training includes mandatory completion of the CITI Human Subjects and GCP training modules. Documentation of that general training is maintained by the Office of Education & Quality in Clinical Research at the Hennepin Healthcare Research Institute. RVs must also attend two mandatory orientation sessions about expectations for appropriate conduct when volunteering in the ED as well as research fundamentals including informed consent and proper research form completion. Research coordinators document attendance for these orientation sessions. In addition, RVs receive study specific hands-on training and a handbook which describes the specific study and data collection information, and then they receive in-person instruction on study specific details by the research coordinators, PI, or senior research volunteers. The completion of this specific training is kept in either a password protected shared drive or in locked files in the ED. We have documentation that all RVs listed in Observation 4.B received all appropriate training. We acknowledge that it would have been consistent with best research practices to keep the RV training records with the other study related records and will implement this practice going forward.

Corrective Actions Related to Observation # 4:

1. Hennepin Healthcare and [REDACTED] agree that for each study that [REDACTED] serves as a co-principal investigator or sub-investigator, [REDACTED] will be assigned a Research Monitor to review the protocol and case report forms to ensure they properly capture the

- appropriate data points, and then will oversee the conduct of the trials including specific monitoring for accurate and complete record keeping for a period of 3 years.
2. Hennepin Healthcare will change its internal policies to keep training records related to research volunteers, study coordinators, and others on the research staff with the study related records.

Observation # 5:

Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent.

Specifically, for study [REDACTED] there is no identification in source records to show who conducted:

- A. Screening, and completion of Screening Sheets for either study;
- B. Data collection from EMR, and completion of Chart Review form for either study; and,
- C. Data validation, and completion of the AMSS Data Validation form for study [REDACTED]

Response to Observation # 5:

We acknowledge that not all study related forms contained a data field to note the name of the RV who completed the form. However, the main Data Collection form for both studies included data fields to collect the RV's name and their supervisor's name. Of note, the same RV completed all the study forms for an individual subject unless a shift change occurred. Furthermore, the electronic research record-keeping system at Hennepin Healthcare, called REDCap, accurately reflected the names of each RV who collected the data. Thus, while not every study related source document contained the name of the RV who collected the data, [REDACTED] ultimately did accurately retain this information. In the future, we will ensure that all data forms contain a data field for the name of the person recording the information.

Corrective Actions Related to Observation # 5:

1. Hennepin Healthcare will include in its research related policies and processes that all study related data collection case report forms include a data field for the person recording the information on the form.

Observation # 6:

Failure to ensure proper monitoring of the study.

Specifically, there is no documentation to show any monitoring of study [REDACTED]

Response to Observation # 6:

As discussed in response to Observation 1, the PIAS studies were IND-exempt based on 21 CFR 312.2(b) and therefore the regulatory requirements related to sponsor and investigator monitoring at 21 CFR 312.50 and 21 CFR 312.60 are not applicable. However, we do acknowledge that proper monitoring and oversight is essential for appropriate human subject protection, data integrity, compliance with the protocol, Good Clinical Practice, and applicable regulatory requirements.²⁴

Looking to FDA for guidance in this space, we note that FDA's guidance on "Oversight of Clinical Investigations – A Risk Based Approach to Monitoring" makes clear that "the regulations are not specific about how sponsors are to conduct such monitoring and are therefore compatible with a range of approaches to monitoring that will vary depending on multiple factors."²⁵ The guidance also states that "FDA recommends that each sponsor design a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial."²⁶ In these studies, as the study related interventions (use of a stop watch, an agitation scale, and data collection forms) are not associated with safety concerns, using a risk-based approach, the monitoring would be relatively limited. With regard to human subjects protection-related monitoring, [REDACTED] and [REDACTED] research team provided a Notice of Enrollment form to subjects when they were no longer incapacitated. With regard to data integrity risks, [REDACTED] conducted weekly meetings with [REDACTED] research coordinators to discuss data quality control for the study, and the ED staff held Faculty Research Meetings every other week for the investigators to discuss the conduct of their studies. Thus, appropriate monitoring for the studies did occur; it was not, however, clearly documented.

Last, although the drugs used in the PIAS studies were not study related interventions, we also note that there were various clinical monitoring procedures routinely in place for patients in the Special Care Unit of the ED, and all emergency medicine physicians and nurses were trained in proper clinical patient monitoring.

Corrective Actions Related to Observation # 6:

1. To ensure that a specific monitoring plan is developed for each study, described in the protocol, and properly documented during the conduct of the study, a Research Mentor and a Research Monitor will be assigned to [REDACTED] for 3 years.

24 The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) also recommends a risk-based approach. ICH, *Guideline For Good Clinical Practice E6(R1)* at 26 (June 10, 1996), https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.

25 Food and Drug Administration, *Guidance for Industry – Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring* at 2 (Aug. 2013), <https://www.fda.gov/media/116754/download>.

26 *Id.* at 10.

Observation # 7:

Investigational drug disposition records are not adequate with respect to dates, quantity and use by subjects.

Specifically, no clinical investigator-required investigational drug disposition records were maintained for either study [REDACTED]

Response to Observation # 7:

Observation 7 is based on the incorrect premise that the drug products involved in the study were study-related interventions. That is not the case. The drug products used were administered clinically to patients as part of their standard care, and therefore 21 CFR 312.62(a), which requires investigators to maintain drug disposition records, is not applicable. However, even if FDA considers the drug products to be investigational new drugs as used in the ED by its emergency medicine physicians, this regulation regarding drug disposition records would still not be applicable as the PIAS studies are IND exempt under 21 CFR 312.2(b). Thus, [REDACTED] was not required to maintain drug use and disposition records as part of [REDACTED] research. Instead, the Hennepin Healthcare pharmacy maintained this information as per their usual practice for all drug products dispensed for clinical use.

We also note that the fact that the four drug products were obtained for patient use in the ED from the hospital pharmacy through the usual practices of physician ordering and pharmacy dispensing and tracking is further evidence that the drug products were not study related interventions. Accordingly, the hospital did not purchase, or stock drug supplies specific to these research studies.

Corrective Actions Related to Observation # 7:

No corrective actions are planned in response to Observation 7.

Observation # 8:

Lack of records covering receipt and disposition of an investigational drug.

Response to Observation # 8:

Observation 8 is based on the incorrect premise that the drug products that were administered clinically to patients as part of their standard care were study related interventions, and therefore 21 CFR 312.57(a), which requires sponsors to maintain drug disposition records, is not applicable. Even if FDA considers the drug products to be investigational new drugs as used in the ED by its emergency medicine physicians, this regulation regarding drug disposition records would still be inapplicable as the PIAS studies are IND exempt under 21 CFR 312.2(b).

Thus, [REDACTED] was not required to maintain drug use and disposition records. Instead, the Hennepin Healthcare pharmacy maintained this information as per their usual practice for all drug products dispensed for clinical use.

We also note that the fact that the four drug products were obtained for patient use in the ED from the hospital pharmacy through the usual practices of physician ordering and pharmacy dispensing and tracking is further evidence that the drug products were not study related interventions. Accordingly, the hospital did not purchase, or stock drug supplies specific to these research studies.

Corrective Actions Related to Observation 8:

No corrective actions are planned in response to Observation 8.

• • •

With respect to the Corrective Action Plans for Observations 1, 3, 4, 5 and 6 we plan to provide a written update describing our progress in meeting those obligations to FDA in 6 months, at 1 year, and upon full completion. We hope this response adequately addresses the inspectional observations and conveys to you the importance we place on compliance with the applicable regulatory requirements governing clinical research and informed consent.

Lastly, given the complexities of these studies and the apparent confusion of the FDA inspector about our standard clinical practices, we respectfully request to open a dialogue between Hennepin Healthcare and Agency officials to discuss our responses to the inspectional observations. We would welcome the opportunity to meet with Dr. Janet Woodcock, Dr. Robert Temple, Mr. Donald Ashley, Dr. David Burrows, and Ms. Melinda Plaisier.

Thank you for your consideration of our response. Please contact me at [REDACTED] if you need additional information or have any questions.

Sincerely,

[REDACTED]

Hennepin Healthcare

[REDACTED]

Faculty Physician
Department of Emergency Medicine
Hennepin Healthcare System, Inc.

[REDACTED]

Enclosure:

[REDACTED]

Appendix 2—List of references

CC: Dr. David Burrow, Director, Office of Scientific Investigations, Office of Compliance,
CDER

Mr. Donald Ashley, Director, Office of Compliance, CDER



Appendix 2

List of References

Literature Describing Use of Agitation Medications in Emergency Departments as Standards of Care

These are ED-based studies providing the current available evidence for use of olanzapine, midazolam, ziprasidone, and haloperidol for treating agitation.

Olanzapine

Taylor, David Mcd, Celene Y. L. Yap, Jonathan C. Knott, Simone E. Taylor, Georgina A. Phillips, Jonathan Karro, Esther W. Chan, David C. M. Kong, and David J. Castle. 2017. "Midazolam-Droperidol, Droperidol, or Olanzapine for Acute Agitation: A Randomized Clinical Trial." *Annals of Emergency Medicine* 69 (3): 318–26.e1.

Yap, Celene Y. L., David Mcd Taylor, Jonathan C. Knott, Simone E. Taylor, Georgina A. Phillips, Jonathan Karro, Esther W. Chan, David C. M. Kong, and David J. Castle. 2017. "Intravenous Midazolam-Droperidol Combination, Droperidol or Olanzapine Monotherapy for Methamphetamine-Related Acute Agitation: Subgroup Analysis of a Randomized Controlled Trial." *Addiction* 112 (7): 1262–69.

Chan, Esther W., David M. Taylor, Jonathan C. Knott, Georgina A. Phillips, David J. Castle, and David C. M. Kong. 2013. "Intravenous Droperidol or Olanzapine as an Adjunct to Midazolam for the Acutely Agitated Patient: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial." *Annals of Emergency Medicine* 61 (1): 72–81.

MacDonald, Kai, Michael Wilson, Arpi Minassian, Gary M. Vilke, Olga Becker, Kimberly Tallian, Patrice Cobb, Rachel Perez, Barbara Galangue, and David Feifel. 2012. "A Naturalistic Study of Intramuscular Haloperidol versus Intramuscular Olanzapine for the Management of Acute Agitation." *Journal of Clinical Psychopharmacology* 32 (3): 317–22.

MacDonald, Kai, Michael P. Wilson, Arpi Minassian, Gary M. Vilke, Rachel Perez, Patrice Cobb, Kimberly Tallian, Olga Becker, and David Feifel. 2010. "A Retrospective Analysis of Intramuscular Haloperidol and Intramuscular Olanzapine in the Treatment of Agitation in Drug- and Alcohol-Using Patients." *General Hospital Psychiatry* 32 (4): 443–45.

Baldaçara, Leonardo, Marsal Sanches, Daniel Cruz Cordeiro, and Andrea Parolin Jackowski. 2011. "Rapid Tranquilization for Agitated Patients in Emergency Psychiatric Rooms: A Randomized Trial of Olanzapine, Ziprasidone, Haloperidol plus Promethazine, Haloperidol plus Midazolam and Haloperidol Alone." *Revista Brasileira de Psiquiatria* 33 (1): 30–39.

Ziprasidone

- Martel, Marc, Ann Sterzinger, James Miner, Joseph Clinton, and Michelle Biros. 2005. "Management of Acute Undifferentiated Agitation in the Emergency Department: A Randomized Double-Blind Trial of Droperidol, Ziprasidone, and Midazolam." *Academic Emergency Medicine: Official Journal of the Society for Academic Emergency Medicine* 12 (12): 1167–72.
- McDowell, Marc, Kara Nitti, Erik Kulstad, Michael Cirone, Riddhi Shah, Daniel Rochford, Richard Walsh, and Kathleen Hesse. 2019. "Clinical Outcomes in Patients Taking Inhaled Loxapine, Haloperidol, or Ziprasidone in the Emergency Department." *Clinical Neuropharmacology* 42 (2): 23–26.
- Baldaçara, Leonardo, Marsal Sanches, Daniel Cruz Cordeiro, and Andrea Parolin Jackowski. 2011. "Rapid Tranquilization for Agitated Patients in Emergency Psychiatric Rooms: A Randomized Trial of Olanzapine, Ziprasidone, Haloperidol plus Promethazine, Haloperidol plus Midazolam and Haloperidol Alone." *Revista Brasileira de Psiquiatria* 33 (1): 30–39.

Haloperidol

- Nobay, Flavia, Barry C. Simon, M. Andrew Levitt, and Graham M. Dresden. 2004. "A Prospective, Double-Blind, Randomized Trial of Midazolam versus Haloperidol versus Lorazepam in the Chemical Restraint of Violent and Severely Agitated Patients." *Academic Emergency Medicine: Official Journal of the Society for Academic Emergency Medicine* 11 (7): 744–49.
- MacDonald, Kai, Michael Wilson, Arpi Minassian, Gary M. Vilke, Olga Becker, Kimberly Tallian, Patrice Cobb, Rachel Perez, Barbara Galangue, and David Feifel. 2012. "A Naturalistic Study of Intramuscular Haloperidol versus Intramuscular Olanzapine for the Management of Acute Agitation." *Journal of Clinical Psychopharmacology* 32 (3): 317–22.
- MacDonald, Kai, Michael P. Wilson, Arpi Minassian, Gary M. Vilke, Rachel Perez, Patrice Cobb, Kimberly Tallian, Olga Becker, and David Feifel. 2010. "A Retrospective Analysis of Intramuscular Haloperidol and Intramuscular Olanzapine in the Treatment of Agitation in Drug- and Alcohol-Using Patients." *General Hospital Psychiatry* 32 (4): 443–45.
- Baldaçara, Leonardo, Marsal Sanches, Daniel Cruz Cordeiro, and Andrea Parolin Jackowski. 2011. "Rapid Tranquilization for Agitated Patients in Emergency Psychiatric Rooms: A Randomized Trial of Olanzapine, Ziprasidone, Haloperidol plus Promethazine, Haloperidol plus Midazolam and Haloperidol Alone." *Revista Brasileira de Psiquiatria* 33 (1): 30–39.

Midazolam

- Nobay, Flavia, Barry C. Simon, M. Andrew Levitt, and Graham M. Dresden. 2004. "A Prospective, Double-Blind, Randomized Trial of Midazolam versus Haloperidol versus Lorazepam in the Chemical Restraint of Violent and Severely Agitated Patients." *Academic Emergency Medicine: Official Journal of the Society for Academic Emergency Medicine* 11 (7): 744–49.
- Taylor, David Mcd, Celene Y. L. Yap, Jonathan C. Knott, Simone E. Taylor, Georgina A. Phillips, Jonathan Karro, Esther W. Chan, David C. M. Kong, and David J. Castle. 2017. "Midazolam-Droperidol, Droperidol, or Olanzapine for Acute Agitation: A Randomized Clinical Trial." *Annals of Emergency Medicine* 69 (3): 318–26.e1.
- Chan, Esther W., David M. Taylor, Jonathan C. Knott, Georgina A. Phillips, David J. Castle, and David C. M. Kong. 2013. "Intravenous Droperidol or Olanzapine as an Adjunct to Midazolam for the Acutely Agitated Patient: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial." *Annals of Emergency Medicine* 61 (1): 72–81.
- Yap, Celene Y. L., David Mcd Taylor, Jonathan C. Knott, Simone E. Taylor, Georgina A. Phillips, Jonathan Karro, Esther W. Chan, David C. M. Kong, and David J. Castle. 2017. "Intravenous Midazolam-Droperidol Combination, Droperidol or Olanzapine Monotherapy for Methamphetamine-Related Acute Agitation: Subgroup Analysis of a Randomized Controlled Trial." *Addiction* 112 (7): 1262–69.
- Isbister, Geoffrey K., Leonie A. Calver, Colin B. Page, Barrie Stokes, Jenni L. Bryant, and Michael A. Downes. 2010. "Randomized Controlled Trial of Intramuscular Droperidol versus Midazolam for Violence and Acute Behavioral Disturbance: The DORM Study." *Annals of Emergency Medicine* 56 (4): 392–401.e1.