Inspections, Compliance, Enforcement, and Criminal Investigations

Advocate Health Care 6/1/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

June 1, 2012

VIA UPS

Ref: 12-HFD-45-05-03

Joal M. Hill, J.D., M.P.H., Ph.D.
IRB Chairman
Advocate Health Care
205 West Touhy Avenue, Suite 203
Park Ridge, IL 60068-4201

Dear Dr. Hill:

This letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your Institutional Review Board (IRB) between November 7, 2011, and November 30, 2011, by Mr. Bradley J. Maunder, representing FDA. The purpose of this inspection was to determine whether the IRB procedures for the protection of human subjects complied with Title 21 of the Code of Federal Regulations (CFR), Parts 50 and 56. These regulations apply to clinical investigations of products regulated by FDA.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research, to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected. We are aware that at the conclusion of the inspection, Mr. Maunder presented and discussed with you Form FDA 483, Inspectional Observations.

From our review of the establishment inspection report, the documents submitted with that report, and your written responses dated December 19, 2011; April 26, 2012; and May 8, 2012, we conclude that the IRB did not adhere to the applicable statutory requirements and FDA regulations governing the protection of human subjects. We wish to emphasize the following:

The IRB failed to ensure that informed consent would be sought from each prospective subject or the subject's legally authorized representative in accordance with and to the extent required by 21 CFR Part 50 [21 CFR 56.111(a)(4)].

In order to approve research subject to FDA's regulations, an IRB must determine that all of the requirements listed under 21 CFR 56.111 are satisfied. Among other things, the IRB must determine that informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by 21 CFR Part 50. [21 CFR 56.111(a)(4)]

The Advocate Health Care IRB failed to comply with 21 CFR 56.111 when it approved Study 4257, "The Effect of Etomidate on Patient Outcomes after Single Bolus Doses," without requiring that

informed consent be sought in accordance with and to the extent required by 21 CFR Part 50. More specifically, the IRB approved Study 4257, a clinical investigation for which informed consent was not sought from prospective subjects or their legally authorized representatives, without satisfying the requirements for approving such an investigation under 21 CFR 50.24.

We note that in your December 19, 2011, written response to the Form FDA 483, you stated that, until FDA's November 2011 inspection, the IRB did not "make a connection" that FDA's regulations applied to Study 4257. According to a timeline prepared by the IRB during the November 2011 inspection, the IRB took the following actions with respect to this study:

- On December 11, 2006, the IRB approved Study 4257 as a chart review study, in which subjects requiring intubation in the emergency room would be treated according to standard o care, and clinical outcome data would be collected from their medical records. The December 11, 2006, IRB approval letter for this chart review study states that the study was "reviewed and approved as expedited, with HIPAA Waiver and Consent Waiver."
- On July 11, 2007, the clinical investigator submitted an amendment to Study 4257. The amendment proposed randomizing study subjects to receive either midazolam or etomidate, which are both approved drugs, prior to intubation.
- On September 7, 2007, the IRB approved the amendment to Study 4257 and allowed the clinical investigation to continue with the waiver of consent left in place.

Once the clinical investigator proposed that Study 4257 would randomize subjects to receive either midazolam or etomidate, the drugs were no longer being used in the course of medical practice. Accordingly, the study became a clinical investigation subject to FDA regulations, and the IRB was required to review the study in accordance with the requirements of 21 CFR Part 56, including determining that informed consent would be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by 21 CFR Part 50.

We acknowledge the IRB's corrective action plan as outlined in your December 19, 2011, written response, which includes (1) revising the IRB's Policies and Procedures (P&P) to be consistent with FDA regulations with respect to reporting serious unanticipated problems and noncompliance to FDA other governmental agencies, and Advocate Health Care institutional officials, and the criteria for the approval of emergency research; (2) educating IRB members with respect to FDA regulatory requirements for informed consent; (3) posting educational newsletters on the IRB's website; and (4) including a workshop on emergency research at Advocate Health Care's 2012 conference on "Achieving Excellence in Clinical Research." In addition, we acknowledge your April 26, 2012, correspondence summarizing the implementation of this corrective action plan, by providing the revisions made to various sections of the IRB's P&P; dates of meetings in which educational sessions have been, or will be, held; and a copy of the April 2012 IRB newsletter.

You also submitted a response to FDA on May 8, 2012, which included a protocol deviation form for Study 4257 and a copy of a letter that the clinical investigator mailed to subjects enrolled in Study 4257 after the study was completed. The protocol deviation form states that the clinical investigator's letter was intended to explain Study 4257 to the subjects. Your response indicated tha the protocol deviation form and the clinical investigator's letter were filed with the IRB, but were not routed to the appropriate IRB staff member for processing and review. Your May 8, 2012, response further indicated that the protocol deviation form and the letter would be placed on the agenda for the May 22, 2012, IRB meeting.

However, your response is unacceptable because it indicates that the IRB did not review the letter provided to subjects, to determine whether it provided appropriate information to subjects regarding the study, either before the letter was sent to subjects or upon receipt of the letter in the IRB office on November 30, 2011. In addition, we find the clinical investigator's letter to the subjects to be deficient because, among other things, it did not (1) inform the subject unambiguously that he/she was enrolled in a research study, or (2) include details of the study and other information that shoul have been contained in the informed consent document, including information about risk to the subject.

Moreover, it was the IRB's responsibility to determine that informed consent would be sought from

each prospective subject or the subject's legally authorized representative, in accordance with and t the extent required by 21 CFR Part 50, before approving the 2007 amendment to Study 4257. The IRB's failure to meet this responsibility is particularly concerning because the concept of informed consent is fundamental to the conduct of ethical research.[1]

This letter is not intended to be an all-inclusive list of deficiencies for the protocols reviewed and approved by the IRB. It is your responsibility to ensure that Advocate Health Care IRB's practices and procedures comply fully with all applicable statutes and regulations.

Within fifteen (15) business days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future.

Failure to explain the violations noted above adequately and promptly may result in regulatory actio without further notice.

We recommend that you visit the following FDA webpage for information on human subject protections that may assist you in your efforts to bring the IRB into compliance with FDA regulations

http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm[1]

We appreciate the cooperation shown to FDA Investigator Maunder during the November 2011 inspection. If you have any questions, please contact Patrick McNeilly, Ph.D., at 301-796-2941; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Patrick J. McNeilly, Ph.D.
Acting Branch Chief, Human Subject Protection Branch
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 2266
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely,

/S/

Leslie K. Ball, M.D.
Acting Office Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
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Cc: Mr. James H. Skogsbergh
President and Chief Executive Officer
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Ann Errichetti, M.D.
President, Advocate Condell Medical Center
801 South Milwaukee Avenue
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[1] See, e.g., Protection of Human Subjects; Informed Consent, 44 FR 47713 (Aug. 14, 1979); "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research"

(1979), available at http://ohsr.od.nih.gov/guidelines/belmont.html#gob1[2].

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Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

Links on this page:

1. http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm
2. http://ohsr.od.nih.gov/guidelines/belmont.html#gob1