U.S. Department of Health & Human Services

U.S. Food and Drug Administration
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U.S. Food & Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Our Lady of Bellefonte Hospital 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-45-05-02]

Kevin Halter, FACHE
Chief Executive Officer
Our Lady of Bellefonte Hospital
St. Christopher Drive
Ashland, KY 41101

Dear Mr. Halter:

Between January 3, 2012, and January 6, 2012, Ms. Karen Bryerton-Cooper, representing the U.S. Food and Drug Administration (FDA), inspected the Institutional Review Board (IRB) at Our Lady of Bellefonte Hospital. 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. We are aware that at the conclusion of the inspection, our investigator presented and discussed with you and other staff members a Form FDA 483, Inspectional Observations. We acknowledge receipt of the IRB's January 20, 2012, written response to the Form FDA 483.

From our review of the establishment inspection report and the documents submitted with that report, 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:

1. The IRB failed to prepare and maintain adequate documentation of written procedures for the IRB, as required by 21 CFR 56.108(a) and (b) [21 CFR 56.115(a)(6)].

An IRB is required to prepare and maintain adequate documentation of written procedures for a variety of IRB functions and operations, in accordance with 21 CFR 56.108. The IRB failed to adhere to these requirements. Specifically, the Our Lady of Bellefonte Hospital IRB policies and procedures do not include written procedures to address the following functions and operations:

a. Reporting the IRB's findings and actions to the investigator and the institution;

b. Determining which projects require review more often than annually, and which projects need verification from sources other than the investigator that no material changes have occurred since the previous IRB review;

c. Ensuring that changes in approved research, during the period for which IRB approval has alread been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects;

d. Ensuring prompt reporting to the IRB of changes in research activity;

e. Ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB;

f. Ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of any unanticipated problems involving risks to human subjects or others;
and

g. Ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of any suspension or termination of IRB approval.

The IRB's written response to the Form FDA 483, dated January 20, 2012, states that the IRB has drafted new policies and procedures, and that it will educate IRB members on these processes. However, the new policies and procedures submitted with this response have not received final approval from the IRB. In addition, the IRB's statement that it will educate IRB members on the processes is inadequate because it does not describe the process that the IRB will use to train and educate IRB members and staff on these regulatory requirements, nor does it provide projected completion dates for the training of the IRB members and staff. Without this information, FDA cannot conduct an informed evaluation of the proposed corrective and preventative action's potential ability to prevent the recurrence of these or similar violations in the future.

2. The IRB failed to prepare and maintain a list of IRB members identified by name; earned degrees; representative capacity; indications of experience sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution [21 CFR 56.115(a)(5)].

An IRB is required to maintain a list of IRB members in accordance with 21 CFR 56.115(a)(5). The IRB failed to adhere to this requirement. Specifically:

a. The 2009, 2010, and 2011 membership rosters do not identify members by earned degrees; representative capacity; indications of experience sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution.

b. The January 5, 2010, membership roster does not include Dr. **(b)(6)** Dr. **(b)(6)**, and Ms. **(b)(6** as IRB members. However, IRB meeting minutes for the July 13, 2010, meeting indicate that they attended this meeting and voted on research.

c. The January 21, 2009, membership roster does not include Dr. **(b)(6)** and Ms. **(b)(6)** as IRB members. However, IRB meeting minutes for the October 28, 2009, meeting indicate that they attended this meeting and voted on research.

The IRB membership rosters are not updated as changes in membership occur. Therefore, the FDA is unable to determine that the IRB is duly constituted, as required by 21 CFR 56.107.

The IRB's written response to the Form FDA 483, dated January 20, 2012, states: "A list containing this information has been created and is now being maintained by the Clinical Trials Coordinator." This response is inadequate because the IRB does not describe the actual process that the IRB will use to ensure that the IRB prepares and maintains a list of IRB members in accordance with the regulations at 21 CFR 56.115(a)(5). As a result, the FDA is unable to undertake an informed evaluation of the proposed corrective and preventative action's potential ability to prevent the recurrence of these or similar violations in the future.

3. The IRB failed to prepare and maintain adequate documentation of IRB activities [21 CFR 56.115(a)(1), (2), and (4)].

An IRB is required to prepare and maintain adequate documentation of IRB activities including, but not limited to, copies of progress reports submitted by investigators; minutes of IRB meetings in sufficient detail to show the vote on IRB actions; and copies of all correspondence between the IRB and the investigators. The IRB failed to adhere to this requirement. Specifically:

a. The IRB does not maintain copies of progress reports submitted by investigators.

b. Minutes of IRB meetings do not show the votes on IRB actions, including the number of members voting for, against, and abstaining.

c. The IRB does not maintain copies of correspondence between the IRB and the investigators.

Maintaining records, as required under the regulations, provides significant evidence of whether the procedures utilized by the IRB are adequately protecting the human subjects of the clinical investigations that the IRB is reviewing.

The IRB's written response to the Form FDA 483, dated January 20, 2012, states that the IRB has drafted new policies requiring progress reports by investigators and the communication of IRB actions. In addition the IRB's response indicates that it has revised its IRB policy titled "Membership/Meetings/General Functions." However, the new policies and procedures submitted with the January 20, 2012, written response have not received final approval from the IRB. In addition, the IRB's statement that it will educate IRB members on the process is inadequate because it does not describe the process that the IRB will use to train and educate IRB members and staff on these regulatory requirements, nor does it provide projected completion dates for the training of the IRB members and staff. Without this information, FDA cannot conduct an informed evaluation of the proposed corrective and preventative action's potential ability to prevent the recurrence of these or similar violations in the future.

4. The IRB failed to review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas [21 CFR 56.108(c)].

Except when an expedited review procedure is used, the IRB may only review proposed research at convened meetings at which a majority of the IRB members is present, including at least one member whose primary concerns are in nonscientific areas. The IRB failed to adhere to these requirements. Specifically:

a. The IRB meeting minutes for July 13, 2010, indicate that five voting members were present and six voting members were absent at the meeting. Despite the IRB's not having a majority of voting members present, it reviewed and approved a revision to Study **(b)(4)**, all serious adverse events, and conducted continuing review and granted approval for Studies **(b)(4)**.

b. It is unclear if at least one voting member was a nonscientific member at convened IRB meetings As discussed in Violation 2 above, the IRB membership rosters for 2010 and 2011 are inadequate, and the FDA is unable to determine, based on the IRB meeting minutes, if the required nonscientist was present at all convened IRB meetings.

The IRB's written response to the Form FDA 483, dated January 20, 2012, states that the IRB has changed its existing policy to require that a majority of voting members be present for all meetings. However, the draft policies and procedures submitted with this response have not received final approval from the IRB. In addition, the IRB's statement that it will educate IRB members on the process is inadequate because it does not describe the process that the IRB will use to train and educate IRB members and staff on these regulatory requirements, nor does it provide projected completion dates for the training of the IRB members and staff. Without this information, FDA cannot conduct an informed evaluation of the proposed corrective and preventative action's potential ability to prevent the recurrence of these or similar violations in the future.

5. The IRB failed to notify investigators and the institution in writing of its decision to approve or disapprove proposed research activities, or of modifications required to secure IRB approval of the research activity [21 CFR 56.109(e)].

An IRB is required to notify investigators and the institution in writing of its decision to approve or disapprove proposed research activities. The IRB failed to adhere to this requirement. Specifically, review of the IRB's files for Studies **(b)(4)** found no documentation that investigators were notified of the IRB approval for those studies.

The IRB's written response to the Form FDA 483, dated January 20, 2012, states that the IRB has drafted a new policy that will notify the investigator and institutional officials of its decisions in a timely manner. However, the new policies and procedures submitted with this response have not received final approval from the IRB. In addition, the IRB's statement that it will educate IRB members on the process is inadequate because it does not describe the process that the IRB will use to train and educate IRB members and staff on these regulatory requirements, nor does it provide projected completion dates for the training of the IRB members and staff. Without this information, FDA cannot conduct an informed evaluation of the proposed corrective and preventative action's potential ability to prevent the recurrence of these or similar violations in the future.

6. The IRB failed to follow FDA regulations regarding expedited review procedures [21 CFR 56.110(b)].

The regulations require that under an expedited review procedure, the review may be carried out by the

IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB; and the IRB may use the expedited review procedure to review either or both of the following: (1) Some or all of the research appearing on the Federal Register list of categories of research eligible for expedited review and found by the reviewer(s) to involve no more than minimal risk; or (2) minor changes in previously approved research during the period for which approval is authorized.

Furthermore, as stated in the Federal Register notice, an expedited review procedure may be used for continuing review as follows:

- Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
- Where no subjects have been enrolled and no additional risks have been identified; or
- Where the remaining research activities are limited to data analysis.

The IRB Lady of Bellefonte Hospital IRB failed to comply with 21 CFR 56.110(b) when it used expedited continuing review for research that was not eligible for approval through an expedited review procedure. Specifically:

The IRB Certification Sheet dated July 12,2011, documents that the IRB used an expedited review procedure for the continuing review and approval of Study **(b)(4)**, titled "**(b)(4)**." The rationale given on the IRB Certification Sheet for the approval of this study under an expedited review procedure states: "Expedited Review due to majority voting memebers (sic) not available for meeting."

Our inspection revealed that the continuing review of Study **(b)(4)** was not eligible for expedited review because one subject had been enrolled in the study at the time of the expedited review, and the study was still open for subject accrual. Therefore, Study **(b)(4)** should have been reviewed and approved at a convened meeting with a majority of the IRB members present.

As this observation was not listed in the Form FDA 483, the IRB's written response did not address this finding. Please provide a written response that details a corrective action plan to ensure that the IRB will use the expedited review procedure in accordance with 21 CFR 56.11 O(b). In this response, submit a cop of any revised or new Standard Operating Procedures (SOPs) developed to address this finding, and any additional actions taken, such as the training of the IRB members, to demonstrate that the proposed corrective action will prevent any future recurrence of this type of violation.

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 Our Lady of Bellefonte Hospital 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 bring the IRB into full compliance with FDA regulations. Your written response should address each citation in the letter and include any documentation necessary to show that full and adequate correction will be achieved. Please include the projected completion dates for each action to be accomplished. Failure to explain the violations noted above adequately and promptly may result in regulatory action 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 Ms. Cooper during the 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
Food and Drug Administration

Cc: Kevin Howard, D.O.
Chairman, Institutional Review Board
Our Lady of Bellefonte Hospital
St. Christopher Drive
Ashland, KY 41101

Links on this page:

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

- Advisory Committees
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- Regulatory Information
- Safety
- Emergency Preparedness
- International Programs
- News & Events
- Training and Continuing Education
- Inspections/Compliance
- State & Local Officials
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