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Inspections, Compliance, Enforcement, and Criminal Investigations

[REDACTED], IRB 9/21/12



Department of Health and Human Services

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

WARNING LETTER

SEPT 21, 2012

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

Dear [REDACTED]:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection of your Institutional Review Board (IRB) that was conducted between April 11, 2012, and April 23, 2012, by Ms. Myra K. Casey, 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 ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Ms. Casey presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of the IRB's written response dated April 23, 2012, to the Form FDA 483. From our review of the FDA's establishment inspection report, the documents submitted with that report, and the IRB's written response, 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 determine at the time of initial review that studies involving children are in compliance with 21 CFR Part 50, Subpart D, Additional Safeguards for Children in Clinical Investigations [21 CFR 56.109(h)].

Under 21 CFR 56.109(h), when some or all of the subjects in a study are children, the IRB must determine that the research study is in compliance with 21 CFR part 50, subpart D (Additional Safeguards for Children in Clinical Investigations) at the time of initial review. Under 21 CFR 50.50, an IRB may approve only those clinical investigations that satisfy the criteria described in 50.51 (clinical investigations not involving greater than minimal risk), 50.52 (clinical investigations involving greater than minimal risk but presenting the

prospect of direct benefit to individual subjects), or 50.53 (clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition).

Under 21 CFR 50.51, 50.52, and 50.53, the IRB must make and document certain findings. Our inspection revealed that in its review and approval of research involving pediatric subjects, Memorial Hospital of South Bend IRB failed to adequately find and document that the research satisfied the criteria of 50.51, 50.52, or 50.53. Specifically, the following pediatric studies were reviewed and approved by the IRB, but the IRB records do not specify whether the study was approved under 50.51, 50.52, or 50.53:

- "(b)(4) for the Prevention of (b)(4)"

This study remains open for data analysis.

- "(b)(4)"

This is an open study.

- "(b)(4)"

This is an open study.

We acknowledge the IRB's written response, which includes the following corrective actions: (1) Developing a checklist for pediatric studies; (2) including a discussion of 21 CFR 50, Subpart D in the IRB meeting minutes; (3) performing a Subpart D review at the time of continuing review of pediatric research; and (4) incorporating these procedures into the IRB's written procedures. The IRB's response is inadequate because it does not contain a 21 CFR 50, Subpart D determination for the three studies listed above; it does not contain copies of the written procedures; and it does not contain a time frame for when the IRB anticipates the implementation of these new procedures.

Please submit the IRB's Subpart D determinations for each of these studies; a copy of your written procedures, or any draft procedures in development; and a timeline for the implementation of any new procedures. In addition, please provide a description of any training provided to IRB staff on the new procedures and a list of attendees, or a projected timeline of planned training.

Failure to determine that the additional safeguards for children in research are met may expose this vulnerable population to unnecessary risks and result in the child's parent(s) or guardian(s) not being fully informed about the proposed research.

2. The IRB failed to prepare, maintain, and follow required written procedures governing the functions and operations of the IRB [21 CFR 56.108(b) and 21 CFR 56.115(a)(6)].

In order to fulfill the requirements of the IRB regulations, each IRB must prepare, maintain, and follow written procedures describing IRB functions and operations specified in the regulations.

The IRB's "Policy and Procedures Manual" does not include all the required written procedures. Specifically, the IRB does not have procedures to ensure prompt reporting to the IRB, appropriate institutional officials, and the FDA of:

- unanticipated problems involving risks to human subjects or others;
- any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; and
- any suspension or termination of IRB approval.

We note that the Form FDA 483 did not include an observation related to the lack of procedures for the

reporting of any suspension or termination of IRB approval, and therefore this issue was not addressed in your corrective action plan. However, we acknowledge the IRB's corrective action plan that promises prompt notification to FDA and the president of the institution, and revisions to the written procedures, for the reporting of (1) serious or continuing noncompliance with FDA regulations, and (2) unanticipated problems involving risks to human subjects or others. The IRB's response is inadequate because it does not include a copy of the revised written procedures.

Please submit a copy of your written procedures, or any draft procedures in development, and a timeline for the implementation of any new procedures. In addition, please provide a description of any training provided to IRB staff on the new procedures and a list of attendees, or a projected timeline of planned training.

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

An IRB shall prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings, which shall be in sufficient detail to show attendance at the meetings, actions taken by the IRB, the vote on these actions, including the number of members voting for, against, and abstaining, the basis for requiring changes in or disapproving research, and a written summary of the discussion of controverted issues and their resolution. Your IRB failed to adhere to the above-stated regulations. Examples of this failure include, but are not limited to, the following:

a. According to two separate letters sent by the IRB to the clinical investigator, both dated June 3, 2009, the IRB approved two versions of the revised informed consent documents (dated "12/30/08" and "05/07/09") for the study "(b)(4)" at the June 3, 2009, meeting. However, neither of these approvals is recorded in the minutes of the June 3, 2009, IRB meeting, which states only that there was approval of an amendment "related to the simplification of blood draws."

b. Furthermore, the record copy of the "5/7/09" version of the informed consent document for the study "(b)(4)" is stamped with an approval date of "8/5/09." As noted above, the IRB sent an approval letter dated June 3, 2009, indicating approval of this same document at the June 3, 2009, meeting. Moreover, approval of the "5/7/09" version of the informed consent form is not recorded in the minutes of the August 5, 2009, IRB meeting. The approval recorded in the minutes pertains to continuing review of this study. Based on this discrepancy in the IRB's records, it is unclear if this informed consent document was approved on June 3, 2009, as stated in the approval letter, or on August 5, 2009, as stamped on the document.

c. The June 3, 2009, IRB meeting minutes reflect IRB review of a new protocol entitled "(b)(4)." However, the minutes document that a motion was made and seconded "to approve study for an *additional* year" (emphasis added). Based on this discrepancy in the IRB's records, it is unclear if this the initial review or a continuing review.

The IRB's written response indicates that these problems stemmed from a failure to inform the full board of research approved by the expedited review procedure. The response also states that since October 2011, all expedited review items have been discussed with the full board at the next convened meeting; the response also promised revisions to the written procedures to include this procedure. The IRB's response is inadequate because it does not include a copy of the revised written procedures.

Please submit a copy of your written procedures, or any draft procedures in development, and a timeline for the implementation of any new procedures. Please provide a description of any training provided to IRB staff on the new procedures and a list of attendees, or a projected timeline of planned training.

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 [21CFR 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:

Minutes of the February 4, 2009, IRB meeting indicate that the following members were present: **(b)(6)** (registered nurse); **(b)(4)** (physician); George Maher (physician); **(b)(6)** (registered nurse); and **(b)(6)** (pharmacist). Therefore, a member whose primary concerns are in *nonscientific* areas was not present at this meeting in which FDA-regulated research (HUD approval, protocol deviations, and adverse events) was reviewed.

We acknowledge the IRB's written response that the IRB is currently recruiting a second nonscientific member, and that the IRB promised that revisions will be made to the written procedures to address this issue. The IRB's response is inadequate because it does not include a copy of the revised written procedures.

Please submit a copy of your written procedures, or any draft procedures in development, and a timeline for the implementation of any new procedures. Please provide a description of any training provided to IRB staff on the new procedures and a list of attendees, or a projected timeline of planned training.

5. The IRB failed to ensure that no member participated in the initial or continuing review of a project in which the member had a conflicting interest, except to provide information requested by the IRB [21 CFR 56.107(e)].

In order to approve research, an IRB must ensure that voting members do not have a conflict of interest in the research. Minutes of the August 6, 2008, IRB meeting indicate that eight members were present, including the Chairman and Dr. George Maher. Dr. Maher was also the clinical investigator for Study **(b)(4)**. The IRB's written procedures indicate that the Chairman does not vote, except to break a tie. At this meeting, the IRB approved Study **(b)(4)** with a vote of 7 in favor, 0 opposed, and 0 abstentions. Therefore, it appears that Dr. Maher participated in the review and approval of his own research.

We acknowledge the IRB's written response that since October 2011, all members of the IRB with a conflict of interest have excused themselves during discussion and voting on actions related to their research, and that the IRB promised revisions to the IRB's written procedures that will explain this procedure in more detail. The IRB's response is inadequate because it does not include a copy of the revised written procedures.

Please submit a copy of your written procedures, or any draft procedures in development, and a timeline for the implementation of any new procedures. Please provide a description of any training provided to IRB staff on the new procedures and a list of attendees, or a projected timeline of planned training.

6. The IRB failed to conduct continuing review of research at intervals of not less than once per year [21 CFR 56.109(f)].

In order to fulfill the requirements of the IRB regulations, an IRB is required to conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year.

An IRB approval letter dated December 14, 2010, indicates that the **(b)(4)** Master Treatment Protocol was approved for continued treatment of the currently enrolled patient for a one-year period beginning December 14, 2010, and expiring December 13, 2011. Our inspection took place in April 2012, and our investigator could find no documentation to indicate the status of this study after IRB approval expired on December 13, 2011.

The IRB's written response states, "This particular study lacks records of initial approval to determine when continuing review is due. It is believed that the study was initially approved on June 2011 which makes the continuing review due June 2012." This statement does not comport with the statements in the approval letter referenced above, or with the information in the table of "open studies" that was provided to the FD/ investigator. According to the information in the table, this study was initially approved by the IRB on December 3, 2008. Your written response also states, "In October 2011, the IRB began the process to review all continuing review on an eleven-month cycle. This will ensure that there are no lapses in continuing review due to meeting dates." The IRB's response is inadequate because this corrective action has failed to address the confusion pertaining to the **(b)(4)** study, and it does not include a copy of the

revised written procedures.

Please submit a corrective and preventive action (CAPA) plan to address the citation above. With your CAPA plan, submit a copy of your written procedures, or any draft procedures in development, and a timeline for the implementation of any new procedures. Please provide a description of any training provided to IRB staff on the new procedures and a list of attendees, or a projected timeline of planned training.

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 Memorial Hospital of South Bend 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. Your written response should 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 Web page 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>

We appreciate the cooperation shown to FDA Investigator Casey during the inspection. If you have any questions, please contact Catherine Parker at 301-796-5553; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Catherine Parker, R.N.
Team Lead, Human Subject Protection Branch
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5247
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely,

/S/

Thomas Moreno, M.S.
Acting Office Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

cc: Ms. Alicia Dombkowski
IRB Chairperson
Memorial Hospital of South Bend
615 North Michigan Street
South Bend, IN 46601

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