Inspections, Compliance, Enforcement, and Criminal Investigations

Covenant Healthcare 9/7/11

Department of Health and Human Services

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

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 11-HFD-45-09-01

Mr. Spence Maidlow
President & Chief Executive Officer
Covenant HealthCare
1447 North Harrison
Saginaw, MI 48602-5383

Dear Mr. Maidlow:

Between April 4, 2011 and April 20, 2011, Ms. L'Oreal F. Walker, representing the Food and Drug Administration (FDA), inspected the Institutional Review Board (IRB) at Covenant HealthCare. 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 John M. Kosanovich, M.D., Vice-President of Medical Affairs, a Form FDA 483, Inspectional Observations.

From our review of the establishment inspection report, the documents submitted with that report, and Dr. Kosanovich's written response dated May 10, 2011, 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 IRB activities including a written summary of the discussion of controverted issues and their resolution [21 CFR 56.115(a)(2)], making it appear that the IRB failed to determine that risks to subjects were minimized and reasonable in relation to anticipated benefits [21 CFR 56.111(a)(1) and(2)].

When a controverted issue arises during the IRB's review of research, they must document the discussion of the issue, and its resolution in the meeting minutes.
Specifically:

The IRB reviewed study # (**b)(4)** ,"(**b)(4)** "at the December 16, 2009 IRB meeting. Minutes from this meeting indicate that an IRB member "questioned if the placebo group of the study would be receiving less than the standard of care in this study since the national professional association was recommending the use of (**b)(4)** currently." The IRB also suggested revisions to the informed consent form, and approved the study pending those changes.

However, after the standard of care for prevention of preterm birth issue was raised, there is no evidence in the correspondence between the IRB and the clinical investigator that the IRB queried the clinical investigator with respect to this issue. We note that a letter dated December 16, 2009 from the IRB to the clinical investigator (that the IRB references in its written response) briefly mentions this issue; however, the IRB merely requests that additional information be added to the "alternative treatments" section of the informed consent form and requests that the informed consent form state that the subject may receive a placebo or the study drug. Finally, the meeting minutes do not document any discussion or its resolution prior to approval at the December 2009 meeting. The IRB identified a potential risk and did not document

discussion of the controverted issue, and its resolution, before approving the research. Thus, it appears that the IRB approved research without making a determination that risks to subjects were minimized and reasonable in relation to the anticipated benefit.

On February 17, 2010, the IRB approved the revised informed consent document. The information added to the revised informed consent form did not address the standard of care issue identified at the December 16, 2009 meeting. In addition, the minutes from the February 17, 2010 meeting do not include any discussion with respect to risks associated with subjects receiving less than the standard of care for prevention of preterm birth.

The IRB's written response states that the IRB reviewed and approved the changes requested with the resubmission of the revised informed consent form on February 15, 2010. In addition, the IRB plans to indicate in its approval letters that requested changes have been adequately addressed by the investigator and study documents have been revised to the IRB's satisfaction.

The IRB's response is inadequate to prevent the recurrence of this, or similar violations in the future. The response fails to address the primary concern documented in the observation. There was a controverted issue with respect to members of a vulnerable population receiving less than the standard of care. There was no record of the discussion of this issue or its resolution. The lack of documentation makes it appear that the IRB approved the study without ensuring that risks to subjects are minimized and reasonable in relation to anticipated benefits. Careful consideration of this issue should impact the IRB's risk/benefit determination, and ultimately, approval of this research study in this vulnerable population.

Although the IRB's response describes plans to change its approval letters, Covenant IRB has not provided documentation as to the specifics of those changes or projected implementation dates. Nor does the response address the failure to document discussion and resolution of controverted issues. As a result, the IRB has failed to provide documentation of corrective and preventative actions sufficient to enable the agency to undertake an informed evaluation of the potential adequacy of the proposed corrective and preventative action's ability to prevent the recurrence of these, or similar violations in the future.

2. 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 process to review either or both of the following: (1) some or all of the research appearing on the Federal Register list 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.

a. The IRB used expedited review for types of research that were not eligible for approval through expedited review. Examples of this failure include, but are not limited to, the following:

- On March 24, 2009, the IRB Chairman granted expedited approval for subject **(b)(6)** who initiated treatment with **(b)(4)** on March 27, 2009 under single-patient IND **(b)(4)**. The IRB did not grant full board approval until April 15, 2009.
- On May 8, 2009, the IRB Chairman granted expedited approval for subject **(b)(6)** who appears to have initiated treatment with **(b)(4)** on May 11, 2009 (date subject signed the ICD; none of the IRB's documents indicate when treatment was initiated). **(b)(4)** received treatment under single-patient IND **(b)(4)**. The IRB did not grant full board approval until June 17, 2009.

The IRB used the expedited review procedure to review and approve the use of **(b)(4)** (an investigational, unapproved drug) in the treatment of pregnant women with recent **(b)(4)** infection under two expanded access protocols.

The use of expedited review for the approval of these studies violates FDA regulations because they involve more than minimal risk and are not a minor change in previously approved research. According to FDA regulations, minimal risk means that 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. The risks associated with receiving an investigational drug are greater than the risks that a person would normally encounter in daily life or when undergoing routine tests.

In reviewing the IRB's draft procedure "Policy for Compassionate/Emergent Use of an Investigational Drug" it appears that the IRB is conflating "emergency use" which is exempt from prospective IRB review and approval, with "compassionate use" now referred to as "Expanded Access."[1] All studies approved under the "Expanded Access" program require prospective IRB review and approval because they are not a type of research eligible for expedited review.

b. On July 13, 2010, the IRB Chairman used the expedited review procedure for the continuing review and approval of study # **(b)(4)**, "**(b)(4)**." Use of the expedited review procedure was not appropriate in this instance because the June 22, 2010, Research Study Update Form indicated that three subjects had been enrolled at Covenant, and the study was still open for subject accrual; therefore, the study did not meet the requirements for continuing review by an expedited review procedure.

The IRB's written response indicates that they used the expedited review procedure because no new information or unanticipated risks were identified prior to the last annual update. However, according to the Federal Register notice, "Protection of Human Subjects: Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure,"[2] the expedited review procedure may only 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 **(b)(4)** study was not eligible for expedited continuing review because the study was open to subject accrual, and enrolled three
subjects.

Even though the clinical investigator requested an expedited review in all three instances discussed above, the IRB must make the determination as to when use of the expedited review procedure is appropriate.

c. In addition, the use of expedited review for the approval of the **(b)(4)** studies violates the IRB's own procedure because the studies involve pregnant women, a population specifically excluded from expedited review by the IRB's Policy and Procedure #9 "Functions of the IRB: Expedited Review", which states "studies involving vulnerable populations (pregnant women…) or focusing on minority populations may not be expedited." The IRB's written response indicates that the IRB disagrees with this observation and maintains that the IRB used the expedited review procedure appropriately in these two instances. This statement directly contradicts the IRB's own procedure, which states that studies involving pregnant women are not eligible for expedited review.

The IRB's written response is inadequate because it does not represent an accurate understanding of the regulations governing expedited review. Specifically, the IRB's response fails to acknowledge that the use of expedited review was improper in all three instances above. As a result, Covenant IRB conducting a thorough review of the expedited review regulations and the appropriateness of your IRB's expedited review process, and re-training of IRB staff is necessary. The IRB has failed to provide documentation of corrective and preventative actions sufficient to prevent the recurrence of this, or similar violations in the future.

3. The IRB failed to ensure that information given to subjects as part of informed consent is in accordance with 21 CFR Part 50.25 [21 CFR 56.109(b)].

The informed consent documents (ICDs) signed by two subjects who were treated with **(b)(4)** were lacking some of the required elements of informed consent.
Specifically:

a. The ICD entitled "consent to receive **(b)(4)** to attempt to prevent **(b)(4)** in my baby" was signed by subject **(b)(6)** on March 27, 2009, and subject **(b)(6)** on May 11, 2009.

The consent forms do not contain statements that the study involves research and lack a description of the procedures to be followed with respect to the investigational drug treatment [21 CFR 50.25(a)(1)]. The statement in the ICD that the "treatment will be discussed with you" does not sufficiently meet the regulatory requirement for a description of procedures.

b. In addition, the ICD signed by subject **(b)(6)** on March 27, 2009, does not contain an explanation of whom to contact for answers to pertinent questions about research subjects' rights [21 CFR 50.25(a)(7)]. The contact information for Covenant HealthCare IRB was left blank.

In response to the observation that the ICD was lacking a statement that the study involves research, the IRB refers to page 5, item #8 under the "Consent Statement" section of the ICD, which states that the subject will be asked to sign forms authorizing the use and disclosure of protected health information in connection with participation in this research. This statement, on its own, does not sufficiently meet the regulatory requirement of disclosing to the subject that the study involves research.

Failure to ensure that all of the FDA required elements of informed consent are met, may result in human subjects not being provided with enough information about a study so that they can give effective informed consent.

4. 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. Our inspection revealed that on numerous occasions, IRB members with a conflict of interest voted on their own research. Examples of instances where IRB members voted on their own research include, but are not limited to, the following:

a. **(b)(4)** is a member of the IRB and a sub-investigator for the **(b)(4)** study. Dr. **(b)(4)** voted for the initial approval of the **(b)(4)**
study at the August 19, 2009 IRB meeting.

Dr. **(b)(4)** also reviewed and approved serious adverse event (SAE) reports for the **(b)(4)** study at IRB meetings held on October 21, 2009, April 21, 2010, and January 19, 2011. Minutes of these meetings indicate that all members present voted to approve the SAE reports.

The IRB's written response acknowledges that meeting minutes do not indicate that Dr. **(b)(4)** abstained from voting on the **(b)(4)** study.

b. IRB Chairman Dennis Boysen, M.D., is the clinical investigator for the study "**(b)(4)**." Dr. Boysen voted to approve the **(b)(4)** study at Continuing Review Subcommittee (CRS) meetings held on November 16, 2009, February 15, 2010, May 17, 2010, August 16, 2010, and November 15, 2010. At subsequent full board meetings, the IRB (including Dr. Boysen) voted to approve the following documents: amended protocol, revised ICD, annual progress report, marketing brochure, and revised Investigator Brochure.

The IRB's written response acknowledges that Dr. Boysen had a conflict of interest and voted at these meetings.

The IRB's corrective action for this observation is a plan to include all coinvestigators on IRB documentation, in addition to primary investigators to provide a second check to ensure that IRB members with a conflict of interest are excused from deliberations and vote, and that the minutes will reflect this practice. The IRB also states that IRB administrative support staff will be educated with respect to this issue. We acknowledge the IRB's commitment to improve documentation of conflicts of interest in the minutes; however, it is not sufficient to provide education only to IRB support staff. IRB members also need to be educated with respect to conflict of interest, including education on the IRB's written procedures, which require that members with a conflict of interest leave the room during both discussion and voting. Lastly, we acknowledge the IRB's plan to document vote tallies for approval of CRS meeting minutes in the minutes of full board IRB meetings.

The IRB's response is inadequate because the IRB has failed to provide documentation of corrective and preventative actions sufficient to enable the agency to undertake an informed evaluation of the potential adequacy of the proposed corrective and preventative action's ability to prevent the recurrence of this, or similar violations in the future. The IRB has not provided documentation of the specific changes to the IRB policy and procedure, a timeframe for implementation, and records of the training which staff has received on these planned changes to IRB policy and procedure.

In addition, we note that the IRB's process for expedited review encompasses: (1) an initial review and approval by an IRB member, (2) review and IRB action at a CRS meeting, (3) presentation of the CRS minutes and IRB action at a full board IRB meeting. The IRB may want to simplify this process by eliminating the multiple layers of review.

5. **The IRB failed to follow its written procedures for conducting continuing review of research [21 CFR 56.108(a)(1)].**

An IRB shall follow its written procedures for conducting its initial and continuing review of research. The IRB has failed to follow their written procedures for continuing review of research. Specifically:

The IRB uses a Continuing Review Subcommittee (CRS) made up of members of the IRB, to accomplish continuing review tasks. The IRB's written procedures state that items such as "annual update/renewal applications" will be presented only in CRS members' monthly materials. We do not consider the CRS to be the same as the IRB. However, we do require that the IRB, and by extension, the CRS, follow written procedures for conducting continuing review of research.

The IRB does not follow its written procedures with respect to CRS continuing review requirements. According to the written procedures, a CRS consisting of three to eight IRB members will meet monthly to accomplish continuing review tasks. The CRS will be comprised of one member whose primary concerns are nonscientific (layperson), one member whose primary concerns are scientific (professional), one pharmacist, one member not affiliated with the institution, the IRB Chairperson or Vice-Chairperson, and the IRB Specialist. The IRB voted to approve the continuation of studies at the following meetings where the CRS did not adhere to the continuing review procedure:

a. Minutes of the April 19, 2010 CRS meeting indicate that two members attended. The IRB's CRS procedure requires a minimum of three members.

b. Minutes of CRS meetings held on July 14, 2008, August 18, 2008, June 15, 2009, April 19, 2010, and November 15, 2010 indicate that a non-scientist did not attend the meetings. The IRB's CRS procedure requires that a nonscientist member be present.

c. There was no documentation of the attendance of an unaffiliated member in any of the CRS minutes. The IRB's CRS procedure requires that an unaffiliated member be present.

We acknowledge the IRB's plan to document vote tallies for review of CRS minutes in the minutes of full board IRB meetings. In addition, the IRB's written response indicates that the general attendance for the CRS meetings averages six members for each meeting and that the IRB agrees that representation of a non-scientific member needs to be consistent. The written response also indicates that the IRB considers **(b)(6)**, IRB Specialist to be a non-scientist. However, according to the 2009,

2010, and 2011 IRB rosters, Ms. **(b)(6)** is a scientific member.

The IRB's response is inadequate because it does not address the IRB's failure to follow procedures for continuing review. The IRB has failed to provide documentation of corrective and preventative actions to prevent the recurrence of this, or similar violations in the future. In addition, the response does not address the absence of an unaffiliated member from the CRS meetings.

Unanticipated risks are sometimes discovered during the course of an investigation, and new information sometimes comes to light showing that the risks in a study are not justified. Periodic review will assure that these risks are promptly brought to the IRB's attention and will provide extra protection to subjects. Consequently, FDA believes periodic review by an IRB is essential if an IRB is to adequately protect the rights and welfare of the human subjects involved in a clinical investigation.

We wish to emphasize that at continuing review the IRB must apply the same criteria for approval as those for its initial approval of the research [21 CFR 56.109(f)]. In conducting continuing review of research not eligible for expedited review, the IRB should receive and review material necessary for these determinations to be made. It appears that the IRB's procedures and practices fail to allow for discussion among the full IRB on protocols undergoing continuing review. Such items should include, but are not limited to:

- a copy of the current version of the protocol in use at the site
- a copy of the current informed consent document in use at the site
- the Investigator's Brochure, if available
- a status report on the progress of the research to include:
    - o the number of subjects accrued
    - o the number of subject withdrawals
    - o a description of any adverse events or unanticipated problems involving risks to subjects or others
    - o a summary of any recent literature findings obtained thus far
    - o amendments or modifications to the research since the last review
- any other relevant information, especially information about risks associated with the research.

For more information on this topic, please refer to the draft guidance, "Guidance for IRBs, Clinical Investigators, and Sponsors: IRB Continuing Review after Clinical Investigation Approval".[3]

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 Covenant HealthCare 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 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 adequately and promptly explain the violations noted above 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[1]

We appreciate the cooperation shown to FDA Investigator Walker during the inspection. If you have any questions, please contact Patrick J. 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
Bldg 51, Room 2266
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely,

{See appended electronic signature page}
Leslie K. Ball, M.D.
Acting Director
Office of Scientific Investigations
Office of Compliance

Center for Drug Evaluation and Research
Food and Drug Administration

cc: John M. Kosanovich, M.D.
Vice-President of Medical Affairs
Covenant HealthCare
1447 North Harrison
Saginaw, MI 48602-5383

Dennis Boysen, M.D.
IRB Chairman
Covenant HealthCare
1447 North Harrison
Saginaw, MI 48602-5383

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic
signature.

/s/

LESLIE K BALL
09/07/2011
Reference ID: 3011043

[1] For information on this topic see:
http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccesstoInvestigationalDrugs/ucm176098.htm

[2] A link to the Federal Register notice is located at:
http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm118099.htm

[3] A link to the draft guidance is located at:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM197347.pdf

---

Links on this page:

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