U.S. Department of Health & Human Services

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Inspections, Compliance, Enforcement, and Criminal Investigations

Christian Hospital Northeast-Northwest 3/27/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852-1448

March 27, 2012

By Facsimile Transmission and Overnight Delivery

CBER- 12- 02

Ronald B. McMullen, President
Christian Hospital Northeast-Northwest
11133 Dunn Road
St. Louis, Missouri 63136

Warning Letter

Dear Mr. McMullen:

This letter describes the results of a Food and Drug Administration (FDA) inspection of the Christian Hospital NE-NW Institutional Review Board (IRB) that concluded on December 2, 2011. The FDA investigator conducted the inspection of this Institutional Review Board (IRB) to determine if the IRB's procedures for the protection of human subjects comply with FDA regulations published in Title 21, Code of Federal Regulations (CFR), Parts 50 and 56. The FDA conducted this inspection under its Bioresearch Monitoring Program, which includes inspections designed to review IRB operations for clinical studies of investigational products and for the protection of human subjects.

At the end of the inspection a Form FDA 483, Inspectional Observations, was issued and discussed with you anc several IRB staff members. We reviewed the inspection report, the Form FDA 483 and your letter dated December 21, 2011 sent in response to the Form FDA 483.

We have determined that the IRB significantly violated applicable federal regulations governing the operation and responsibilities of the IRBs as published under 21 CFR Part 56 (available at http://www.gpoaccess.gov /cfr/index.html). The applicable provisions of the CFR are cited for each violation. We are addressing this lette to you because, under 21 CFR 56.120(c), the parent institution is presumed to be responsible for the operation of the IRB. As the parent institution, it is within your responsibility to ensure that the IRB takes the actions necessary to bring the IRB into full compliance with FDA regulations.

1. The IRB failed to prepare, maintain and follow its written procedure for conducting its initial and continuing review of research. [21 CFR §§ 56.108(a) and 56.115(a)(6)].

The IRB did not adhere to the procedures and practices established for the IRB in its written procedure entitled "Clinical Research involving Human Subjects and Institutional Review Committee Policy."

A. The IRB failed to maintain attendance sign in sheets as required by the IRB's procedure for the following meetings: 11/23/2009, 5/19/2010, 7/14/2010, 3/1/2011, 8/25/2011 and 11/11/2011.

In your response you proposed to revise the IRB's written procedure to discontinue use of the attendance sign in sheet and replace it with an attendance log managed by the IRB administrator and maintained as an attachment to all meeting minutes. Your corrective actions appear to be adequate if successfully implemented. In your response to this letter please explain what steps the institution has taken to ensure that the revised procedure will be followed given that the IRB did not follow the previous written procedure.

B. A review of the IRB meeting minutes for 2009 through 2011 revealed that the IRB did not consistently have at least one physician member review protocols prior to each meeting. The IRB procedure states, "The entire protocol…. shall be sent for review to at least one (1) physician member reasonably prior to the meeting." In your letter you included a revised agenda template that will prompt the IRB administrator to assign a primary physician reviewer upon receipt of a new protocol. Your corrective actions appear to be adequate if successfully implemented.

C. The IRB allowed a member and his/her alternate to vote at the same convened meeting. The meeting minutes from 11/11/2011 list both the member **(b)(6)** and his designated alternate **(b)(6)** as members present.

In your letter you explained this was a clerical error on the IRB's part and that **(b)(6)** was a regular member during that period. As an attachment to your letter, you submitted a revised membership roster listing **(b)(6)** as a voting member. This implies that the IRB roster at that time was out of date. We remind you that your IRB written procedures require the membership roster to be updated at least annually, dated, and signed by each member and alternate.

D. The IRB meeting minutes between 2010 and 2011 do not document the period of approval for proposed research determined to be appropriate by the IRB after considering the degree of risk. This determination is required under the IRB's written procedures. In your December 21 response, you included a revised meeting agenda template with a designated area for documentin the period of approval. Your corrective actions appear to be adequate if successfully implemented.

The IRB's failure to follow its written procedures is a repeated violation that was identified during the last FDA inspection in 2003. In your letter dated December 21, 2011, you provided a plan of correction that includes several revisions to the IRB written procedure with an anticipated ratification date by the IRB for January 2012. In your response to this letter include a copy of the current revised and approved IRB written procedure(s).

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

A. IRB meeting minutes for 2009 through 2011 were not prepared in sufficient detail to show the vote on the actions taken by the IRB, including the number of members voting for, against and abstaining. The meeting minutes used the term "unanimous" to document the vote actions. According to the IRB Chair, **(b)(6)** the members record their votes (yes, no, or abstain) on a separate voting sheet which is maintained with each protocol. Two of the five protocols reviewed during the inspection did not have voting sheets maintained with the protocol records.

In your letter, you attached a revised meeting minutes/agenda format that will prompt the IRB administrators to record voting numbers and discussion points for future IRB meeting minutes. Your corrective actions appear to be adequate if successfully implemented.

The IRB's failure to maintain meeting minutes in accordance with 21 CFR 56.115(a)(2) is a repeated violation identified in the last two FDA inspections conducted in 2003 and 1998.

B. There are discrepancies between the meeting minutes and the attendance sign-in sheet regarding which members were present.

i. The meeting minutes dated 2/3/2010 list 6 members present including **(b)(6)**, but the attendance sign in sheet has 5 signatures with **(b)(6)** listed as excused.
ii. The meeting minutes dated 11/10/2010 list 7 members present and no excused members, but the attendance sheet has 5 signatures with **(b)(6)** and **(b)(6)** listed as excused.
iii. The meeting minutes dated 5/3/2011 listed 6 members present with **(b)(6)** listed as

excused, the attendance sheet had 5 signatures with **(b)(6)** and **(b)(6)** listed as excused. iv. The meeting minutes dated 7/12/2011 list **(b)(6)** as a member present but the attendance sheet does not have his signature. According to the membership roster for 7/12/2011, **(b)(6)** is an alternate member for **(b)(6)**. **(b)(6)** signature is on the sign in sheet for 7/12/2011 but is not listed as a member present in the meeting minutes for that date.

C. The IRB failed to document in the meeting minutes that a member abstained from voting on a protocol in which the member has a conflict of interest. The meeting minutes dated 5/3/2011 do not document that **(b)(6)** abstained from voting on protocols **(b)(4)** and **(b)(4)**. The protocol review signature sheet, which includes members' signatures and their votes, indicates that **(b)(6)** abstained from voting.

D. The IRB failed to maintain IRB membership rosters for 2010 and 2011 in accordance with 21 CFR 56.115(a)(5). The IRB membership rosters do not accurately reflect current IRB membership. Furthermore, the rosters do not identify members by their representative capacity, and any employment or other relationship between each member and the institution. In your letter, you provided a revised membership roster lacking an effective date in 2011. Additionally, it is not signed by each member as required by the IRB's written procedure. In your response to this lette please provide an updated membership roster that is in compliance with the IRB written procedure

The IRB's failure to maintain IRB membership rosters in accordance with 21 CFR 56.115(a)(5) is a repeated violation identified in the last two FDA inspections conducted in 2003 and 1998.

In your letter dated December 21, 2011, you provided a plan of correction that included a revised meeting minutes/agenda format and a new attendance log that is a required attachment to the future IRB minutes. In your response to this letter, please submit a copy of the IRB's meeting minutes for all meetings conducted to date in 2012 to demonstrate successful implementation.

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

A. The IRB voted on new protocols, reviewed reports of adverse events, and conducted periodic review of studies on at least four meeting dates, 11/23/2009, 5/19/2010, 3/1/2011 and 5/3/2011 at which a majority of IRB members were not in attendance.

No. of IRB members on roster	Meeting date	No. of IRB members present	Comment
12	11/23/2009	5	
10	5/19/2010	5	
10	3/1/2011	5	**(b)(6)** is listed as a member present in the minutes but was not listed on the membership roster in effect for that time period so she should not have been counted toward a majority
10	5/3/2011	5	**(b)(6)** is listed as a member present in the minutes but was not listed on the membership roster in effect for that time period so she should not have been counted toward a majority

B. The IRB approved new research protocols on 3/1/2011 and 5/3/2011 when there was no member present whose primary concerns are in nonscientific areas. As noted in the table located i Item 3.A., above, **(b)(6)** is listed as a member present at the meetings held on 3/1/2011 and 5/3/2011 but was not an IRB member according to the membership roster in effect for that time period. As a result, **(b)(6)** should not have been allowed to vote, count toward a majority, or be considered to be the IRB's nonscientific member. We remind you that the IRB minutes and membership roster must accurately reflect IRB membership. The membership roster must be updated as changes occur.

In your letter dated December 21, 2011, you submitted a new attendance log as the corrective action for this observation. According to your letter, the attendance log was created to sufficiently address meeting attendance, document when individual members log in and out of the meeting as well as to identify individual member roles (i.e. voting or nonvoting). Your corrective actions appear to be adequate, if successfully implemented.

This letter is not intended to contain an all-inclusive list of deficiencies in the operations of the IRB. Throughout

this letter we have identified several repeated violations noted during previous FDA inspections conducted in 2003 and 1998. In your response to this letter please explain how the institution will ensure that the IRB takes the actions necessary to bring the IRB into full compliance with FDA regulations.

Please notify this office in writing, within fifteen (15) business days of receipt of this letter, of the actions you have taken or plan to take to bring the IRB into compliance with FDA requirements. Please include a copy of any revised documents, such as written procedures and recent meeting minutes, with your response. Given the past failure to follow written procedures, please also describe your plans to assure compliance with your revised procedures.

Your failure to adequately respond to this letter and take appropriate corrective action may result in further administrative actions against your IRB, as authorized by 21 CFR 56.120 and 56.121. These actions could include FDA withholding approval of new studies reviewed by your IRB that are subject to 21 CFR Parts 50 and 56 of the FDA regulations, prohibiting the admission of new subjects to ongoing studies that are subject to Parts 50 and 56, terminating all ongoing studies approved by your IRB, and initiating regulatory proceedings for disqualification of your IRB.

Please send your written response to:

Lillian Ortega
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448
Telephone: (301) 827-6335

Sincerely,

/s/

Mary A. Malarkey, Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc: John Thorsky, District Director
Food and Drug Administration
11510 West 80th Street
Lenexa, Kansas 66214

Kristina Borror, Ph. D., Director
Division of Compliance Oversight
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Rockville, Maryland 20852

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