

Inspections, Compliance, Enforcement, and Criminal Investigations

Centra Health Inc Irb



Department of Health and Human Services

Public Health Service
Food and Drug
Administration
10903 New Hampshire
Avenue
Silver Spring, MD 20993

WARNING LETTER

NOV 20 2009

George W. Dawson, President and CEO
Centra Support Building
1920 Atherholt Rd.
Lynchburg VA 24501

Dear Mr. Dawson:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection of your Institutional Review Board (IRB) from September 1 to September 14, 2009, by an investigator from the FDA Baltimore District Office. The purpose of this inspection was to determine whether your IRB is in compliance with applicable federal regulations. IRBs that review investigations of devices must comply with applicable provisions of Title 21, Code of Federal Regulations (21 CFR) Part 56-Institutional Review Boards, Part 50-Protection of Human Subjects, Part 312-Investigational New Drug Applications and Part 812-Investigational Device Exemptions. This letter also requests prompt corrective action to address the violations cited and discusses Thomas C. Jividen's, Executive Vice President, and Chairman of the IRB. September 30, 2009 written response to the noted violations.

The inspection was conducted under a program designed to ensure that data and

information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval (PMA) applications, and Premarket Notification submissions (510(k)) are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report prepared by the district office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR) Part 56 -- Institutional Review Boards. At the close of the inspection, the FDA investigator presented an inspectional observations form FDA 483 for review and discussed the observations listed on the form with Mr. Thomas C. Jividen and Ms. Elizabeth R. Burgess, Executive Assistant, Secretary of the IRS. The deviations noted on the FDA 483, Mr. Jividen's written response on behalf of the IRB, and our subsequent review of the inspection report are discussed below:

Failure to conduct continuing review of research at least annually. [21 CFR 56.109(f)].

An IRB shall conduct continuing review of research covered by these regulations at

intervals appropriate to the degree of risk, but not less than once per year.

Examples of

this failure include, but are not limited to, the following:

- The IRB did not conduct continuing review of the study entitled, **(b)(4)**" until **(b)(4)** via expedited retroactive re-approval though the study was due for continuing review on **(b)(4)**.
- The IRB did not conduct continuing review of the study entitled, **(b)(4)**

Review of FDA regulated studies are to be conducted at intervals appropriate to the degree of risk, but no less than once per year; therefore, the practice of retroactive review is improper. Mr. Jividen's response to this deviation, noted that a two-fold system involving a spreadsheet and e-mail calendar has been developed to remind the IRB when a study is due for renewal. The response is inadequate, in that he did not provide evidence of the spreadsheet as well as its date of implementation. Please provide documentation and the date of implementation of your corrective actions.

Failure to ensure that the IRB reviews proposed research at convened meetings at which a majority of the members are present (21 CFR 56.108(c))

A majority of IRB members, including at least one member whose primary concerns are in the nonscientific area, is needed to review proposed research at

convened meetings. Examples of the failures include, but are not limited to, the following:

- During the meet that occurred on January 26, 2007, the IRB approved the study entitled, "(b)(4)." However, the minutes for that meeting reflect that the IRB had (b)(4) members present though one of the members, Ms. (b)(6) who abstained, had a conflicting interest in a research study being reviewed. Ms. (b)(6) abstention was counted toward the majority of the membership present during the IRB's review of that study when she should have been excluded in the total count of voting members.
- During the meeting that occurred on May 11, 2007, Ms. (b)(6) and Ms. (b)(6) abstained from voting on three FDA studies (b)(4), in which one or the other served as study coordinator. However, both abstentions were counted towards the majority of membership, (b)(4) when they should have been excluded from the total count of IRB members present at the convened meeting.

In the above, the IRB lost its majority necessary to review the above FDA regulated research. The abstentions resulted in only (b)(4) members present for the purpose of voting on each of the above studies.

In Mr. Jividen's response, he indicated that Centra Health IRB will monitor its quorum more closely in future meetings. He also noted that an abstention does not break quorum under applicable rules and so long as a majority of the quorum approves a motion, the motion passes. Please note that FDA regulations require review of proposed research at convened meetings at which a majority of the members of the IRB are present and in order for the research to be approved, it shall receive the approval of a majority of those members present. A majority is defined as more than fifty percent of the total voting members of an IRB (excluding alternates). No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. Thus, in the above cases, the IRB membership did not maintain the required majority to review FDA regulated studies. The response is inadequate in that Mr. Jividen has not provided a corrective action to prevent this violation from reoccurrence. Please provide a proposed plan for addressing this violation in your response to this letter.

Failure 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 the following: minutes of IRE meetings which shall be in sufficient detail to show attendance at all meetings; actions taken by the IRB; and the vote of these actions including the number of members voting for, against, and

abstaining.

- Meeting minutes dated, May 11, 2007 and May 16, 2008 reflect that the IRB documented approval or unanimous approval on actions rather than documenting the actual numbers of members who voted for, against or abstained during voting periods.

In Mr. Jividen's response, he indicated that the IRB minutes will be more detailed immediately and will continue to be so in the future. The response is inadequate in that he has not provided a corrective action to prevent this violation from reoccurrence. Please provide evidence of the corrective actions that you have implemented (e.g. SOPs, copies of recent meeting minutes) and the prospective dates of implementation for such changes.

Failure to have adequate written procedures governing the functions and operations of the IRB 121 CFR 56.108(a)(2) and 21 CFR 56.108(b)(1)(2)].

An IRB must prepare, maintain and follow written procedures that describe the IRB's functions and operations, including: conducting continuing review of research; 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 previous IRS review; ensuring that changes to approved research may not be initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to the human subjects; and ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of unanticipated involving risks to human subjects. The IRB's written procedures entitled " **(b)(4)**," last reviewed by the IRB in January 2000, lacked procedures for the following:

- Ensuring prompt reporting to the IRB, institutional officials, and the FDA of unanticipated problems involving risk to human subjects, of instances of noncompliance with the regulations, and of suspension or termination of IRB approval;
- Determining which projects require review more often than annually and for projects that need verification from sources other than the investigator that no material changes have occurred since the previous IRS review.

In the response, Mr. Jividen's states that he agreed that the IRB's policies and procedures need to be improved and he indicated that a subcommittee was formed to modify the policy and procedure manual. The response is inadequate in that he has not provided any evidence of the proposed plan (e.g. SOPs), date of implementation for such plan, and proposed training to educate IRB members about the plan being implemented. Please provide documentation of all actions

taken to correct these deficiencies.

Please note that your policies and procedures, section subtitled "**(b)(4)**" (pg 7), states that an "**(b)(4)**" Officials of an institution may not approve research if it has not been approved by an IRB as per 21 CFR 56.112.

The violations described above are not intended to be an all inclusive list of problems that may exist at the IRB. The IRB is responsible for ensuring compliance with the Act and applicable regulations.

Within fifteen (15) working days of receiving this letter, please provide written documentation of the actions you have taken or will take to correct these violations and prevent the recurrence of similar violations. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. Send your response to: Attention: Levering Keely, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 9200 Corporate Boulevard, HFZ-310, Rockville, Maryland 20850.

A copy of this letter has been sent to 6000 Metro Drive, suite 101, Baltimore, Maryland 21215. Please send a copy of your response to that office.

The Division of Bioresearch Monitoring has developed introductory training modules in FDA regulated device clinical research practices, which are available on the FDA website. The modules are for persons involved in FDA regulated device clinical research activities. These modules are located at the following website address: <http://www.fda.gov/Training/CDRHLearn/ucm162015.htm>

If you have any questions, please contact Levering, Keely, BSN, MPA, at 301-796-5490 or via e-mail at Levering.Keely@fda.hhs.gov.

Sincerely yours,

/S/

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health