Inspections, Compliance, Enforcement, and Criminal Investigations

Valley Health/Winchester Medical Center IRB 5/9/13

Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

May 9, 2013

WARNING LETTER

VIA UNITED PARCEL SERVICE

Mark H. Merrill
President & Chief Executive Officer
Valley Health
P.O. Box 3340
Winchester, VA 22604

Dear Mr. Merrill:

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 January 29, 2013, to February 1, 2013, by an investigator from the FDA Baltimore District Office. This inspection was conducted 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 (CFR) Part 56 - Institutional Review Boards, Part 50 - Protection of Human Subjects, and Part 812 - Investigational Device Exemptions. This letter also requests prompt corrective action to address the violations cited and discusses your IRB's written response dated February 11, 2013, 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 applications, and premarket notification submissions 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 repeated violations of 21 CFR Part 56 - Institutional Review Boards, which concerns requirements prescribed under section 520(g) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360j(g). At the close of the inspection, the FDA investigator presented a Form FDA 483, Inspectional Observations, for your review and discussed the observations listed on the form with you. The deviations noted on the Form FDA 483, the IRB's written response,and our subsequent review of the inspection report, are

discussed below:

1. **Failure to follow FDA regulations regarding the expedited review procedures. [21 CFR 56.110(b)(2)]**

The FDA regulations for IRBs require that, under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced IRB members designated by the IRB chairperson. The regulations state that 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 that may be reviewed by the IRB through an expedited review procedure and found by the reviewers to involve no more than minimal risk; and (2) minor changes to previously-approved research.

Your IRB is in violation of this regulation, which does not extend to significant risk device studies currently under an IDE. These studies did not meet the criteria of minimal risk and the changes in the protocol were not minor. Therefore, they were not eligible for expedited review according to the Federal Register list of research categories that may be reviewed by the IRB through an expedited review procedure. Examples of deficiencies include, but are not limited to, the following:

- For the study entitled **(b)(4)** your IRB approved the protocol amendments #6 and #7 and revised the informed consent under expedited review. The changes included the **(b)(4)** to the list of potential adverse events to study subjects. **(b)(4)** are serious medical conditions that could affect the risk to study subjects and represent a major change in the research and should not be reviewed using the expedited review procedure. Furthermore, your IRB allowed Ms. Deborah Moore, IRB Manager, to approve the protocol amendment involving the **(b)(4)** as an adverse event under expedited review. Ms. Moore does not possess the experience and background to perform this critical task. Major changes in research should be reviewed by a full IRB board whose members have the necessary diversity and expertise to evaluate these changes. This is critically important for a complete and adequate review of research and to ensure the protection of human research subjects.
- For the study entitled **(b)(4)**, your IRB approved the protocol and informed consent amendments II and III under expedited review that allowed the **(b)(4)** and the **(b)(4)** in the study. These amendments, especially the use of additional devices, represent major changes in the research. Your use of the expedited review procedure was not appropriate because it precluded your IRB from conducting a thorough review of these changes to identify any additional risks to subjects. This is a critical step in ensuring that appropriate human subject protection measures are in place to help mitigate those risks.

Your IRB's non-compliance is a repeat violation. A 2008 FDA inspection revealed instances where your IRB inappropriately reviewed research that was not minor in nature under expedited review. On March 17, 2009, FDA forwarded your IRB the publication, "Clinical Investigations Which May Be Reviewed Through Expedited Review Procedure," which describes the different categories of research that may be reviewed under expedited review. Your IRB included information from this document in its standard operating procedures (SOPs) entitled, "Valley Health/Winchester Medical Center IRB Policies and Procedures" revised June 11, 2012, and dated February 8, 2013. Therefore, your IRB should have been aware of the categories of research that are eligible for expedited review.

Your IRB's response states that Dr. Sears determined that some of these protocol changes would not affect the safety of study participants and therefore did not require a full board review. This response is inadequate and does not provide the assurance that your IRB fully understands which research changes are appropriate for expedited review and which are required to be evaluated by a full board

Your IRB's response also included revised procedures that we deem inadequate. The SOP states that any initial protocol submissions or amendments that are related to "patient care," other than

"administrative changes," will be forwarded to the IRB Chair to determine if the changes qualify for expedited review. This SOP is inadequate in that there is no assurance that major changes in research will not be misinterpreted as "administrative" or minor in nature. Your IRB's SOPs are not specific enough to consider the impact and risk that such changes may have on study subjects and informed consent documents. Please revise your IRB's SOPs and forward a copy of this revision, along with training records, a list of staff trained, and dates of implementation.

2. **Failure to follow written procedures for conducting an initial and continuing review of research. [21 CFR 56.108(a)(1)]**

An IRB shall follow written procedures for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution.

Your IRB failed to follow its SOPs for conducting expedited reviews as part of its initial review of research. Specifically, the June 11, 2012, version of the SOPs states, "A list of documents submitted to the VH/WMC IRB for expedited review will be disseminated at each IRB meeting for review and acknowledgement by Board members. This review and acknowledgement will be documented in the IRB meeting minutes." As a result of failing to follow these SOPs, the full board was not informed of the following changes approved under expedited review: 1) the informed consent for the *NEST-3 Trial* was amended to include hemorrhagic transformation stroke; 2) a second treatment arm was added to the *Mobility 08-107 trial;* and3) subjects were notified of protocol changes to include additional study procedures and medical chart reviews.

It is essential that the full IRB is aware of research reviewed under expedited review procedures. This ensures that the IRB's review of research is conducted completely and adequately with the benefit of the full board members' diverse expertise. Not adhering to the above regulation could expose study subjects to significant risk of harm and potentially compromise the scientific integrity and reliability of research data submitted to FDA in support of marketing applications.

Your IRB's response is inadequate since it does not provide assurance that the IRB understands that all research reviewed under expedited review must be reported back to the full IRB board. The revised SOPs do not contain sufficient instructions on steps to take to ensure expedited reviews are appropriately communicated back to the full board. Also, the response mentioned the use of an "Amendment Form" to facilitate this process; however, this form is not mentioned in the revised procedure. Please revise your IRB's SOPs and forward a copy of this revision, along with training records, a list of staff trained, and dates of implementation.

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 15 working days of receiving this letter, please provide documentation of the additionalaction that your IRB has taken or will take to correct these violations and prevent the recurrence of similar violations, and a plan to monitor the effectiveness of your IRB's corrective actions. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to your IRB.
Your response should reference "CTS # EC120622/E001 and be sent to:

Attention: Veronica J. Calvin, MA
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
10903 New Hampshire Avenue
Building 66, Room 3508
Silver Spring, Maryland 20993-0002

A copy of this letter has been sent to FDA's Baltimore District Office, 6000 Metro Drive, Suite 101, Baltimore, MD 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[1].

If you have any questions, please contact Veronica Calvin at (301) 796- 5647 or Veronica.Calvin@fda.hhs.gov.

Sincerely yours,
/S/
Steven D. Silverman
Director
Office of Compliance
Center for Devices and
Radiological Health

cc:

Ms. Jennifer Stanford, Director of Clinical Research
Richard Sears, MD, IRB Chairman
Valley Health/Winchester Medical Center IRB
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Kristina C. Borror, Ph.D.
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Page Last Updated: 05/24/2013
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

Links on this page:

1. http://www.fda.gov/Training/CDRHLearn/ucm162015.htm