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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

AUG - 1 2005

Via Federal Express

WARNING LETTER

Mr. L. Joe Austin
Chief Executive Officer
Huntsville Hospital
Institutional Review Committee
101 Sivley Road
Huntsville, Alabama 35801

Dear Mr. Austin:

The purpose of this Warning letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection of your institutional review board (IRB), and to request immediate action. The inspection was conducted during the period of February 10 and 11, 2005, by an investigator with FDA's New Orleans District Office. The purpose of the inspection was to determine if the IRB had implemented corrective actions assured in their response to an April 11, 2003 Warning Letter from the FDA and if the IRB is presently functioning in compliance with applicable FDA regulations. IRBs that review studies involving FDA-regulated medical devices must comply with applicable regulations found in Title 21, Code of Federal Regulations (21 CFR) Part 56, Institutional Review Boards; Part 50, Protection of Human Subjects; and Part 812, Investigational Device Exemptions.

Our review of the inspection report, which was prepared by the district office, revealed that serious violations of applicable regulations continue to persist even though the IRB agreed to take corrective action based upon the April 11, 2003 Warning Letter. At the close of the inspection, the FDA investigator presented a Form FDA 483, "Inspectional Observations," to you for review and discussed the listed violations. The violations noted on the Form FDA 483 and our subsequent review of the inspection report are discussed below.

Failure to follow written procedures for IRB functions and operations in accordance with 21 CFR Part 56.108(a) and (b), 21 CFR 56.115(a)(6), and 21 CFR 812.66.

Pursuant to the above stated regulations, each IRB shall prepare, maintain, and follow written procedures for conducting its initial and continuing review of research and written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of any unanticipated problems involving risks to human subjects. In addition, if the IRB determines that an investigation, which was presented to the IRB as a non-significant risk (NSR) device study, involves a significant risk (SR) device study, it shall notify the investigator and where appropriate the sponsor.

The IRB's failures to adhere to their standard operating procedures (SOPs) include but are not limited to the following:

- The IRB SOPs state "each protocol will be addressed separately and a separate vote on each is required and will be documented in the meeting minutes." However, a review of the Institutional Review Committee Minutes dated February 8, 2005, revealed that the IRB reviewed and voted on new information on several protocols and an exception to one protocol as a block vote rather than as individual items as indicated in the SOPs. Block voting (i.e., voting once to approve the continuation of several research protocols) violates your IRB's procedures. Each FDA-regulated research study must be individually reviewed and discussed, and the Board should vote to approve, disapprove, or require changes for approval separately for each research study.

- The SOP entitled, "Procedures for Institutional Review Committee," states that "if a device protocol is being considered, the Committee will review the Investigational Device Exemption (IDE) (if applicable) and make a determination as to whether the device under review poses a significant versus non-significant risk to the patient. This will be documented in the meeting minutes." This procedure fails to adequately describe the review of device studies. For example, the IRB only has to make a SR or NSR determination for device studies presented as NSR studies to the IRB for review. A non-significant risk device will not have an IDE to review. The IRB should use the sponsor's brief explanation (21 CFR 812.2(b)(1)(ii)) of why the device is not a significant risk device when making the SR or NSR determination. In addition, to help the IRB in making the SR or NSR determination, the IRB should review the significant risk definition (21 CFR 812.3(m), the description of the device, and any other material the IRB requests from the sponsor. If the IRB determines the NSR device study to be NSR the IRB may proceed with its review in accordance with 21 CFR 56. However, if the IRB determines the proposed NSR study is a significant risk, then the IRB must notify the investigator and the sponsor if necessary.

  Generally, device studies that are significant risk have already received FDA approval of the IDE application before the study is reviewed by the IRB. In this case, an IRB may want to verify FDA's approval by requesting a copy of FDA's IDE approval letter from the clinical investigator, who will obtain it from the sponsor. Guidance regarding the continuing review process and significant risk vs non-significant risk medical device studies is available in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators which can be found at http://www.fda.gov/oc/gcp/guidance.html.

Failure to require that information given to subjects as part of informed consent is in accordance with 21 CFR 50.25(a) and 21 CFR 56.109(b).

Pursuant to the above stated regulations, in seeking informed consent, the IRB must require that the following information shall be included in the information provided to each subject: an explanation of whom to contact for answers to pertinent questions about the research and the research subjects' rights; and whom to contact in the event of a research-related injury. Your failure to adhere to the above stated regulations includes but is not limited to the following:

- The IRB approved consent for the [redacted] study does not provide a contact for answers to questions regarding subjects' rights. Specifically, the contact phone number for "information regarding this informed consent" is outdated and the number is now disconnected; yet no addendum/information sheet for subjects was observed;

- [redacted] informed consent Version A dated 7/29/04 was approved by the IRB on 11/11/04, even though this consent contained blanks to be filled in for the investigator's name and the contact's names and numbers;

The deviations described above are not intended to be an all-inclusive list of deficiencies. The IRB is responsible for adhering to each relevant requirement of the law and regulations.

As a result of the IRB's continued noncompliance with FDA regulations, in accordance with 21 CFR 56.120(b)(1) and (2), FDA will withhold approval of new studies subject to 21 CFR Part 56 that are reviewed by your IRB. In addition, we direct that no new subjects are to be admitted to ongoing studies subject to 21 CFR Part 56 that are currently under review by your IRB. These restrictions will remain in effect until you are notified in writing by FDA that the IRB's corrective actions are satisfactory.

Within fifteen (15) working days after receiving this letter, please provide written documentation of the specific steps you have taken or will take to assure that the violations noted will not be repeated. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking additional regulatory action without further notice to you. Please send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch (HFZ-312), 2094 Gaither Road, Rockville, Maryland 20850. Attention: Viola Sellman, Chief, Program Enforcement Branch.

We are also sending a copy of this letter to the FDA's New Orleans District Office, 6600 Plaza Drive, Suite 400, New Orleans, Louisiana 70127. We request that a copy of your response also be sent to the New Orleans District Office.

Sincerely yours,

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