DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Blvd.
Rockville MD 20850

APR 23 2008

WARNING LETTER

Via Federal Express

Haring J. W. Nauta, MD
UTMB Galveston
301 University Blvd.
Galveston, TX 77555-5302

Dear Dr. Nauta:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your clinical site from February 12 through 14, 2008, by an investigator from the FDA Dallas District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation as a clinical investigator in the clinical study titled [redacted] under IDE [redacted], sponsored by [redacted], complied with applicable federal regulations. The [redacted] is a device as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h). This letter also requests prompt corrective action to address the violations cited and discusses your March 27, 2008, 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 several serious violations of Title 21, Code of Federal Regulations (21 CFR) Part 812 -- Investigational Device Exemptions and Part 50 -- Protection of Human Subjects. 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 FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

1. **Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50 [21 CFR 50.20 and 50.27(a)].**

   Investigators are responsible for ensuring that informed consent is obtained using an IRB-approved consent document prior to performance of any study-related procedures. The IRB

approval letter for this study, dated March 7, 2000, provided you with a copy of the consent form with the date of the IRB approval stamped on it, and stated, "Please use this copy of the consent form with the IRB approval date and make additional copies as they are needed." You failed to ensure that the current, IRB-approved, version of the informed consent was executed by each of the subjects prior to their participation in the study. Examples of this failure include, but are not limited to, the following:

a.) Two of the subjects you enrolled and randomized into the study signed an unapproved version of the consent form. The IRB-approved informed consent form was a 4-page document stamped with "IRB Mar 7 2000" on the first page, and required the signatures of the study subject, a witness, and the principal investigator. The forms signed by Subjects and were 2-page documents that were substantially different from the IRB-approved version.

b.) Subject signed a consent form that did not contain the IRB approval stamp.

2. **Failure to ensure an investigation is conducted in accordance with the signed agreement with the sponsor, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by FDA or the IRB [21 CFR 812.100 and 21 CFR 812.110(b)].**

You failed to adhere to the above-stated regulations. Examples of this failure include, but are not limited to, the following:

a.) The study protocol requires clinical, , and evaluations preoperatively, immediately post-operatively, at , and , and thereafter until the last subject in the study is . The study sponsor notified you by letter dated January 12, 2004, that you should "continue to follow-up the patients already enrolled for the study, as per the protocol." Only one of the subjects you enrolled in the study have had any study visits beyond the follow-up point, even though subjects are still being enrolled into this study at other sites.

b.) Criteria for measuring success of the study device include evidence of of the involved Follow-up visits and procedures were not performed for subjects in the study as required by the study protocol. For example:

i. Subject – and , and – were not performed or not recorded on the case report forms (CRFs). Also, the follow-up visit was not performed.

ii. Subject – and and , and were not performed or not recorded on the CRFs. Also, the follow-up visit was not performed.

iii. Subject – and were not performed or not recorded on the CRFs. Also, the and follow-up visits were not performed.

iv. Subject – and were not performed or were not recorded on the CRFs.

In your written response, you stated that [redacted] were taken "as per the protocol" but "appropriate documentation was not noted in the case report form" due to the resignation of your study coordinator. This is not an acceptable response. As a Clinical Investigator, you are responsible for ensuring that all study staff are adequately trained and qualified to perform study tasks delegated to them. You may delegate study tasks to other qualified personnel, but you may not delegate your responsibility to ensure that all study tasks are correctly performed.

c.) The study protocol specifically excludes subjects with "[redacted]." The study records for Subject [redacted] indicate existence of [redacted] and this subject should not have been included in the study.

d.) The study protocol requires that post-operative complications and surgeries, whether device-related or not, be recorded and reported on the "[redacted]" CRF. Subject [redacted], and [redacted], which required surgical correction. However, the "[redacted]" CRF for this subject was crossed out, notated "[redacted]," and dated by you on 2/8/08.

e.) You allowed IRB approval for the study to lapse after February 28, 2003. Specifically, the study protocol requires that you submit [redacted] progress reports on the study to your IRB. In addition, the IRB renewal of approval letter, dated [redacted], notes "this project will require [redacted] review by the IRB and will be due by February 28, 2003." The IRB sent you several reminders about the continuing review requirement, to which you failed to respond. The IRB ultimately terminated the study on [redacted], due to your lack of response. Yet you continued to perform study followup visits on enrolled subjects after that date.

In addition, the study protocol states, "should the IRB withdraw its approval, [redacted] Investigator will [redacted]." Federal regulation also requires that an investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB [21 CFR 812.150(a)(2)]. Further, you are required to maintain records on all correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports [21 CFR 812.140(a)(1)]. There was no documentation in your study records to indicate that the FDA and the study sponsor were notified of the IRB termination.

3. **Failure to maintain accurate, complete, and current records relating to your participation in the investigation [21 CFR 812.140(a)].**

You failed to adhere to the above-stated regulation. Examples of this failure include, but are not limited to, the following:

a.) You failed to maintain accurate, complete, and current records of receipt, use, or disposition of the study device, as required by 21 CFR 812.140(a)(2). The study protocol requires that "[redacted]." The FDA investigator observed that you had

no shipping records in your files to document the type and quantity of the investigational devices received by you, the dates of receipt, and the batch numbers or serial numbers of the devices. There were also no records of the number of investigational devices returned to the study sponsor.

b.) You failed to maintain accurate, complete, and current records of each subject's case history and exposure to the device, as required by 21 CFR 812.140(a)(3). Specifically:

i. The "Withdrawal from Study" CRF for Subject [redacted] notes that the subject was lost to follow-up, with the explanation "patient did not return after [redacted] visit." This form was signed by you on 2/9/08. However, a CRF was completed for this subject for the [redacted] followup visit on [redacted]

ii. You failed to record radiographic information on the CRFs for all [redacted] enrolled subjects at the time of the procedures, and the films were subsequently discarded by the hospital after 5 years, per their policy. Federal regulations require that you maintain all study records for a minimum period of 2 years following completion of the entire study [21 CFR 812.140(d)].

In your response, you stated that UTMB has developed an action plan to respond to the inspection findings, which includes "specific" training to be received by you, use of a well-trained study coordinator, receipt of notification by the IRB that only the IRB-approved and stamped informed consent forms may be used, and training regarding the proper conduct of investigative device studies. This response is not acceptable. Please provide us with documentation of a corrective action plan, such as a written procedure for ensuring study protocol compliance and compliance with applicable federal regulations, written verification of training received by you and your study staff on study procedures and requirements, and/or internal study reviews or audits to ensure that such protocol violations have not occurred with other subjects and/or other studies, and that corrective actions have been implemented to prevent recurrence of the problems for future studies. Please also provide us with a plan for future studies that will ensure you can adequately supervise study personnel and procedures that are performed at your site.

The violations described above are not intended to be an all inclusive list of problems that may exist with your clinical study. It is your responsibility as a clinical investigator to ensure 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 in current or future studies for which you are the clinical investigator. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings against you in accordance with 21 CFR: 812.119.

You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at http://www.fda.gov/oc/ohrt/irbs/. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Please send your response to:

Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Bioresearch Monitoring, HFZ-311
9200 Corporate Blvd., Rockville, Maryland 20850
Attention: Ms. Doreen Kezer, Chief, Special Investigations Branch.

A copy of this letter has been sent to FDA's Dallas District Office, 4040 North Central Expressway, Suite 300, Dallas, TX 75204. We request that a copy of your response also be sent to that office.

If you have any questions, please contact Ms. Doreen Kezer at 240-276-0125 or at Doreen.Kezer@fda.hhs.gov.

Sincerely yours,

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