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JUL 13 2004

WARNING LETTER

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

VIA FEDERAL EXPRESS

John Brannon Smoot, M.D.

[REDACTED]
4700 Seton Center Parkway, Suite 200
Austin, Texas 78759

Dear Dr. Smoot:

This Warning Letter informs you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site. This letter also discusses your written response, dated March 25, 2004, to the noted violations and requests that you implement prompt corrective actions. Ms. Brenda Stewart-Munoz, an investigator from FDA's Dallas District Office, conducted the inspection from March 8 through 12, 2004. The purpose of the inspection was to determine if your activities as a clinical investigator for the [REDACTED] study complied with applicable FDA regulations. The [REDACTED] is a device defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321 (h)].

The FDA conducted the inspection under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), and Premarket Notification [510(k)] submissions are scientifically valid and accurate. The program also ensures that human subjects are protected from undue hazard or risk during 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 812-Investigational Device Exemptions, Part 50-Protection of Human Subjects, and Section 520(g) of the Act. At the close of the inspection, Ms. Stewart-Munoz presented a Form FDA 483 "Inspectional Observations" to you for review and discussed the listed deviations with you in the presence of [REDACTED]

The violations noted on the FDA 483 and our subsequent inspection report review as well as your response to the Form FDA 483 items are discussed below:

1. Failure to adhere to informed consent requirements and maintain accurate, complete and current records evidencing informed consent (21 CFR 50.20, 21 CFR 812.100, 21 CFR 812.140(a)(3)(i)).

In accordance with 21 CFR 50.20 and 812.100, clinical investigators are responsible for ensuring that a legally effective informed consent is obtained in accordance with these regulations in order to protect the rights, safety, and welfare of subjects under an investigator's care. Furthermore, investigators must obtain a legally effective informed consent from the subject or the subject's legally authorized representative prior to his or her participation in an investigational study. You failed to satisfy these requirements. For example, you implanted Subject [REDACTED] with the investigational device on July 15, 2003, but that subject did not sign the informed consent form until August 1, 2003.

In your written response to observation 1, item 1 on the Form FDA 483, you indicated that this failure was an oversight in that the patient signed the informed consent form at her postoperative visit and [REDACTED] completed a memo to the file on August 4, 2003 related to this matter. In addition, you indicated that you have taken the following corrective action in response to this failure, that all persons who review subject records for participation in the study and performing the consent process will be re-educated at a study team meeting scheduled on April 2, 2004. This corrective action has been determined acceptable.

Pursuant to 21 CFR 812.140(a)(3)(i), investigators are responsible for maintaining accurate records evidencing informed consent. You failed to satisfy these requirements. For example, the version of the informed consent form (ICF) dated April 14, 2003, which included Health Insurance Portability and Accountability Act (HIPAA) requirements and address change information, was originally submitted to the institutional review board (IRB) with an error indicating the version date as July 19, 2002 rather than April 14, 2003. As a result, [REDACTED] subjects signed an informed consent form which incorrectly indicated its version date.

As of the date of your response, you indicated that you have "reconsented" [REDACTED] of the [REDACTED] subjects and the remaining [REDACTED] subjects' study binders have been flagged to remind staff and yourself of the need to "reconsent" at their next office visit. You expect to have all the subjects "reconsented" by September 2004. Your response does not adequately address our concerns. Please provide FDA with a copy of the subjects signed informed consent forms, and the steps that you plan to take or have taken to prevent the recurrence of not maintaining accurate records related to informed consents.

Your written responses to observation 2, item 2 and observation 3, item 1 on Form FDA 483 indicates that for future enrollment your site will do the following:

- review the subject's history and the inclusion/exclusion criteria during each subject's pre-screen visit;
- if the subject meets the exclusion criteria at the time of the visit, the doctor will discuss postponing the procedure until they qualify for the investigational device or an approved device is available; and
- all staff members reviewing the subjects for participation and involved in the informed consent process have been informed and will be re-educated in the inclusion/exclusion criteria; and a study team meeting will be held on April 2, 2004.

These responses are adequate.

- The 12 month visits for Subject [REDACTED] exceeded protocol timeframes.

In your written response to observation 3, item 2, you indicate that protocol timeframes were exceeded because there was a relocation of your practice and a loss of the study coordinator. You indicated that you have taken the following corrective actions for the failures cited by making an appointment checkout for each of the subjects or having the study coordinator follow subjects due for visits on a monthly basis which entails notifying appointment staff to contact the subject. This corrective action has been determined acceptable.

- There were no [REDACTED]-month x-rays for Subjects [REDACTED], and [REDACTED]

In your response to observation 3, item 5, you indicate that the above subjects were patients of [REDACTED] his standard follow-up care includes an x-ray at the [REDACTED] week post-op visit; and [REDACTED] used the results from the early post-op for completion of the [REDACTED] month post-op x-ray report. Also, you indicated that [REDACTED] will take x-rays at the early post-op and the [REDACTED] month post-op visits as a corrective action. Your actions to prevent future protocol deviations related to the [REDACTED]-month x-rays are adequate; however, your response is incomplete. Please provide the steps that you plan to take or have taken to correct the prior protocol deviations and to notify the sponsor and IRB.

3. Failure to maintain accurate, current and complete records of a subject's case history and exposure to a device (21 CFR 812.140(a)(3))

In accordance with 21 CFR 812.140(a)(3), investigators are required to maintain accurate, current and complete records of each subject's case history and exposure to the device.

You failed to satisfy this requirement. Examples of this failure include but are not limited to the following:

- There was no pre-operative documentation of the [REDACTED] for Subjects [REDACTED] and [REDACTED]. Additionally, the [REDACTED] score for Subject [REDACTED] was out of range or inaccurate.

In your written response to Observation 3, item 1, you acknowledge the findings and state that the first version of the [REDACTED] did not include a method for scoring the [REDACTED] functions but that this has been remedied by the new case report form (CRF) #4, created by the sponsor. You state that the [REDACTED] calculations were reviewed for accuracy and you thus have concluded that the [REDACTED] score for Subject [REDACTED] was miscalculated. While this indicates that the inclusion of Subject [REDACTED] may not have been a protocol deviation, as the [REDACTED] score included in the records inspected by FDA indicated, it demonstrates that those records were not accurate.

- Subjects [REDACTED] and [REDACTED] charts lack documentation for their 3-month visit and 6-month visit, respectively.

You indicate in your response to observation 3, item 3 that although dictated notes of those visits do not appear in the files, you have date stamps and x-rays that document that each of those patients was seen at the appropriate visit. You indicate that as a corrective action, your office now copies the charge slip, routes it to the medical records department, and tracks the slip until dictation is completed and entered into the system. This corrective action should help to prevent repetition of this violation, but does not address how you may supplement the charts for the specific subjects mentioned above to ensure that the date slips and x-rays you mention, as well as any other documentation of their visits, are included.

- Case report forms (CRFs) were not complete. For example, the 6-month visit CRF for Subject [REDACTED] does not contain a [REDACTED] score, and the 3-month visit CRF for Subject [REDACTED] does not document the [REDACTED] or x-rays.

Your response to observation 3, item 4 indicates that these omissions were an oversight. You indicate that future appointments for all study subjects will be

flagged as [REDACTED] in the reason lines of the appointment scheduler to assist the staff in identifying which study binder to pull and make available for the subject's office visit; the study coordinator will also verify the correct scheduling of the appointment; and this will be addressed at the study team meeting on April 2, 2004. Your response to this observation is adequate, however, please provide FDA with copies of the minutes from the April 2, 2004 meeting to verify that this matter was addressed.

The above-described deviations are not intended to be an all-inclusive list of deficiencies that may exist in this clinical study. It is your responsibility as a clinical investigator to assure adherence to each requirement of the Act and all applicable federal regulations.

Within 15 working days after receiving this letter please provide the written documentation of the additional, specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. Any submitted corrective action plan must include projected completion dates for each action to be accomplished.

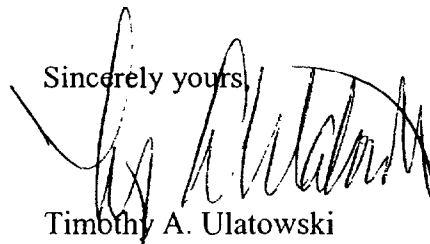
Failure to respond to this letter and to take appropriate corrective action could result in the FDA taking enforcement action without further notice to you. In addition, FDA could initiate disqualification proceedings in accordance with 21 CFR 812.119.

In addition to documenting your corrective actions, please provide a list of your current investigational studies and include the name of the study sponsor and the date of IRB approval.

Send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II, HFZ-312, 2094 Gaither Road, Rockville, Maryland 20850, Attention: Linda Godfrey.

We are also sending a copy of this letter to FDA's Dallas District Office, and request that you also send a copy of your response to that office. If you have any questions, please contact Linda Godfrey by phone at 301-594-4723 extension 134 or by email at linda.godfrey@FDA.HHS.GOV.

Sincerely yours,



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

cc:

[REDACTED] (purged)
General Manager

[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED] (purged)
IRB Chair

[REDACTED]
[REDACTED]
[REDACTED]