



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Public Health Service

WARNING LETTER

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

VIA FEDERAL EXPRESS

JAN 16 2004

James G. Howe, M.D.  
University of Vermont  
College of Medicine  
Robert T. Stafford Hall, Room 436A  
Burlington, VT 05405-0084

Dear Dr. Howe:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site and to discuss Mr. Stephen Terman's October 24, 2003, letter addressed to Gail Costello, District Director, FDA's New England District Office (NWE-DO), responding to your FDA Form 483 observations. We also request a prompt reply describing your corrective actions.

Mr. Garry Stewart and Mr. John Hartford, Investigators from FDA's NWE-DO, conducted the inspection from September 9 through September 17, 2003. The purpose of the inspection was to determine if your activities as a clinical investigator for the [REDACTED] study sponsored by [REDACTED] [REDACTED] complied with applicable FDA regulations. The [REDACTED] [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 [21 U.S.C. 360j(g)]. At the close of the inspection, Mr. Stewart presented a Form FDA 483 "Inspectional Observations" to you for review and discussed the listed deviations. The deviations noted on the Form FDA 483, our subsequent review of the inspection report, and Mr. Terman's response to the Form FDA 483 items are discussed below:

**1. Failure to adhere to the general and specific responsibilities of a clinical investigator [21 CFR 812.100 and 812.110 (b)]**

- a. The protocol required patient follow-up visits at 3, 6, 12, 24, and 48-months post-implantation. The sponsor further required you to complete Status/Contact Forms to document your efforts to locate missing patients. You failed to conduct the study according to the investigational plan by not conducting certain follow up visits or documenting efforts to locate missing subjects. Your records indicated that patient examinations for at least 6 of the 39 subjects were either late or missing, and that there were no Status/Contact Forms completed for those subjects. For example, Patient [REDACTED] missed her 12- and 24-month visits, and there was no record of a 24-month visit for patient [REDACTED]. Patient [REDACTED] was not local and missed the 3- and 6-month visits.

We agree with Mr. Terman that study subjects may fail to complete required follow-up visits. However, the investigational plan required you to document your efforts to conduct timely follow up, and there was no documentation demonstrating that you or your staff made efforts to contact patients who missed their scheduled visits required by the protocol. Complete, timely patient information is essential to support the PMA, and because the 24-month visit was the primary study endpoint, the data were essential for assessing device effectiveness. Patients selected for the study should also be available to complete all study visits. Missing follow up visits may also unnecessarily expose subjects to the risks associated with an investigational device.

- b. You failed to follow the protocol requirement to report all adverse events (AEs) to the sponsor. The protocol states in Section 2.2.1A that “All complications, device-related or not, must be recorded on the application study form and reported to the sponsor.” You failed to report all such complications to the sponsor for at least 9 of the 39 subjects. Among these unreported events were [REDACTED] stiffness, pain, and decreased range of motion reported by patient [REDACTED] at two follow up visits, and [REDACTED] around the implanted device for patient [REDACTED]. The sponsor’s November 1999, December 2000, and September 2001 site monitoring visits documented your failure to report AEs. Some of the adverse events noted by the FDA investigators occurred in 2002 and 2003, even after the sponsor visited your site and informed you that you were not following AE reporting requirements.

We agree with Mr. Terman’s statement indicating that these adverse events may not have met the definition of a reportable, “unanticipated” adverse device event under the regulations. However, we disagree that you did not have an obligation to report these events to the sponsor. The investigational plan expressly required all reports of such complications. Sponsors need the adverse event reports from all study sites to fully assess the relationship between the events and the experimental device and to determine if there is a higher complication rate related to using the device compared to the controls.

- c. You failed to obtain adequate informed consent as described in 21 CFR Part 50 for all subjects. You reported to the FDA that Patient [REDACTED] signed the informed consent form after you conducted the procedure, and your dated signature on that form is 3 weeks after the subject's surgery date. We note that you had reported Patient [REDACTED]'s situation to the IRB and that you have received some human subjects protection training.

**2. Failure to maintain complete, accurate records [21 CFR 21 CFR 812.140(a)(3)]**

- a. Clinical investigators are required to maintain complete, accurate, and current records of each subject's case history and exposure to the device. The Case Report Forms (CRF) for some subjects lacked information relating to the clinical investigation. For example, the CRF for subject [REDACTED] contained blank fields for the total [REDACTED] and other data used to calculate the score. For Patient [REDACTED] the study monitor wrote the [REDACTED] on a self-adhesive note and placed the note in the CRF. The note indicated an [REDACTED] score equal to 42 whereas the line listing on Patient [REDACTED] CRF indicated the score was 25. The [REDACTED] score was an important measure of device effectiveness for this study.
- b. The x-rays and radiology report for patient [REDACTED]'s 24-month visit in 2002 were not included in the subject's file. The patient's Radiographic Evaluation form you signed on September 27, 2002, shortly after [REDACTED]'s 24-month visit was scheduled to take place, indicated that you evaluated the x-rays for this patient's 24-month visit. However, there were no visits for [REDACTED] in 2002 indicated on the hospital's computer printout. According to hospital records, the date of the subject's last visit for x-rays was September 19, 2001 and the printout indicated that the Status of that x-ray report was a "Final Report." Accordingly, it is unclear when those missing x-rays could have been taken.

We disagree with Mr. Terman's statement that [REDACTED]'s missing x-rays and radiology report for the 24-month visit were not a substantial loss for this patient's record. There appears to be no 24-month follow-up data for [REDACTED], although these 24-month data were reported to the sponsor. The primary study end-point was the 24-month data, and the x-rays and radiology report data were essential for assessing device effectiveness.

The deviations listed above are not intended to be an all-inclusive list of deficiencies that may exist at your facility. As an investigator, you are responsible for ensuring that you conduct clinical trials according to FDA regulations.

Please advise this office, in writing, within fifteen (15) working days after receiving this letter of the additional, specific steps you plan to take to correct these violations and prevent the recurrence of similar violations. Failure to respond may result in the FDA taking regulatory action without further notice to you. Please direct your response to the following address: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program

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Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850,  
Attention: Sybil Wellstood, Ph.D.

We are also sending a copy of this letter to FDA's NWE-DO and request that you also send a copy of your response to that office. If you have any questions, please contact Dr. Wellstood by phone at (301) 594-4723, ext. 140, or by email at [saw@cdrh.fda.gov](mailto:saw@cdrh.fda.gov).

Sincerely yours,

A handwritten signature in black ink, appearing to read "Timothy A. Ulatowski". The signature is written in a cursive style with a large initial "T" and a stylized "U".

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

cc:

Stephen D. Terman  
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