



SEP 28 2006

WARNING LETTER

VIA FEDERAL EXPRESS

Randall K. Wolf, MD
University of Cincinnati Medical Center
2600 Clifton Ave., MSB 1466
Cincinnati, OH 45267

Dear Dr. Wolf:

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 April 19 through May 22, 2006, by investigators from the FDA Cincinnati District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the investigator-initiated study titled "[redacted]
[redacted]
[redacted]", and a clinical study titled "[redacted]
[redacted] and [redacted] for the [redacted] (designated herein as the [redacted] study) being conducted in support of PMA [redacted] sponsored by [redacted] complied with applicable federal regulations. The [redacted] that is used for both studies 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 written responses 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 investigators 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 responses, 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, 21 CFR 50.27(a), and 21 CFR 812.100].**

Regarding your investigator-initiated study titled [redacted] and [redacted]

[redacted] you failed to ensure that the current, IRB-approved version of the informed consent was properly executed by each of the enrolled subjects, as required by the above-stated regulations, prior to their participation in the study. Examples of this failure include but are not limited to the following:

- a.) The original signed informed consent forms for all subjects associated with this study were missing because they had been destroyed by the study coordinator or were considered to be lost.
- b.) You told the FDA investigator that the study coordinator has been re-consenting subjects. However, there is no documentation that [redacted] of the [redacted] subjects listed on the enrollment log have been re-consented.
- c.) Subjects [redacted] and [redacted] signed outdated informed consent forms after the IRB expiration date of 08/18/05.
- d.) According to an internal audit report dated 2/21/06, seventeen of the first [redacted] subjects enrolled in the study signed an unapproved informed consent form prior to IRB approval. A response letter sent on your behalf, dated July 10, 2006, states "this discrepancy is being addressed by the research coordinator." Please provide additional information to clarify what is meant by this statement so we can determine if this is an acceptable corrective action.

In addition, the FDA investigators were unable to determine the exact number of subjects who are actually enrolled in this study, in order to verify whether all subjects have been appropriately re-consented. You provided the FDA investigators with a list of [redacted] patients who received this study procedure between 08/19/03 and 05/15/06. It cannot be determined which of these patients were entered into the study as subjects. You told the FDA investigators that [redacted] subjects have been enrolled into the study, and the IRB has approved this study for [redacted] subjects. An "Off-site Monitoring Review Form" dated 1/13/06 notes that [redacted] subjects have been enrolled to date, with [redacted] enrolled prospectively. However, the enrollment log lists only [redacted] subjects, and study files were only available for 33 subjects.

Your June 19, 2006, response notes that the study team is in the process of re-contacting each subject "for the purpose of securing documentation of their provision of legally effective consent." The letter also states, "To date, [redacted] subjects have been enrolled in Study [redacted] and of these, [redacted] are in the retrospective arm." Please provide us with a complete enrollment log listing the correct number of subjects who have been enrolled in this study to date, each subject's initials and assigned study subject number, the date each subject was originally enrolled into the study, the date of each subject's surgical procedure, and the date each subject signed a new consent form.

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, 21 CFR 812.110(b)].**

Regarding the study titled [redacted] and [redacted]

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

- a.) Subject [redacted]:
 - i. Blood pressure and heart rate were not assessed at the 9-minute recovery time during the pre-procedure Exercise Treadmill Test (ETT) as required by the protocol.
- b.) Subject [redacted]:
 - i. Blood pressure was not assessed at the 6-minute recovery time during the pre-procedure Exercise Treadmill Test (ETT) as required by the protocol.
 - ii. The 30-day visit INR was not assessed on 12/1/05 as required by the protocol to assess coagulation status for subjects on anti-coagulants. The subject's medication record notes the subject was taking Coumadin 2.5 mg/day as of 11/4/05.
- c.) Subject [redacted]:
 - i. The pre-operative supine, sitting, and standing blood pressures and heart rates were not assessed as required by the protocol in order to detect postural hypotension.
- d.) Subject [redacted]:
 - i. Laboratory assessments – WBC, HCT, HGB, and Platelets – were not performed prior to hospital discharge as required by the protocol.
- e.) Subject [redacted]:
 - i. The transesophageal echocardiogram (TEE) was not performed within 48 hours of the procedure, as required by the study protocol in order to determine whether clots are present in the left atrium and to evaluate the size of the left atrium.
 - ii. The 3-week cardiac event monitoring was not performed prior to the study procedure as required by the protocol in order to verify asymptomatic AF episodes.
 - iii. The pre-operative supine and standing blood pressures and heart rates were not assessed as required by the protocol in order to detect postural hypotension.
 - iv. Recovery heart rates and blood pressures were not assessed at any time points during the pre-operative ETT as required by the protocol.

The deficiencies noted above are considered to be deviations from the investigational plan (which includes the protocol), and are required by federal regulation [21 CFR 812.150(a)(4)] to be reported to the IRB. In non-emergency situations, prior approval from the IRB is required for such deviations. If you have not already done so, please notify the IRB of the deviations, and any other protocol deviations that may exist with this study. Please provide us with documentation that the IRB has been notified, and any response that you receive from the IRB.

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

Regarding the [redacted] study, you failed to adhere to the above stated regulation. Specifically, there were several inconsistencies between data recorded in the source documents and data recorded in the Case Report Forms (CRFs). Examples of this failure include but are not limited to the following:

- a.) Subject [redacted]:
 - i. The Atrial Fibrillation (AF) History source document records the frequency of episodes in the last 6 months as "≥ 1 daily", while the CRF reports the frequency of episodes in the last 6 months as "≥ 3 episodes in the last 6 months".

- ii. The source document records the AF frequency of symptoms for the last 6 months as "once month, then q 2 wks, then weekly", while the CRF records the AF frequency of symptoms data as "5".
 - b.) Subject [redacted]
 - i. The AF History source document records the frequency of episodes in the last 6 months as "≥ 1 week", while the CRF reports the frequency of episodes in the last 6 months as "≥ 3 episodes in the last 6 months".
 - c.) Subject [redacted]
 - i. Ablation sites for left atria are not recorded on the source record or the CRF.
 - ii. The AF History source document records the AF symptomatic onset date as 6/15/2001 and the duration as 3.5 years. Onset date and duration are blank on the CRF.
 - d.) Subject [redacted]
 - i. The AF History source document records "NO" to the question, "Is AF symptomatic?" and the remaining 3 questions for this section are left blank. The CRF reports "YES" to the AF History question about AF symptoms, and records the onset date as 4/15/2003, the duration as 2 years, and the frequency (symptomatic episodes per month for the last 6 months) as 30.
 - ii. The transesophageal echo (TEE) information for Ejection Fraction is reported as 55% on the source document and 50% on the CRF.
 - iii. The Left Atrial Size is reported as 4.1cm on the source document and is not reported on the CRF.
 - iv. The surgical procedure number of ablations (right side) is reported as 6 ("III + 2") on the source document and "4" on the CRF. The right pulmonary vein further ablation time (minutes) is reported as "2 (+ bipolar)" on the source document and as "6" on the CRF.
 - v. The surgical procedure number of ablations (left side) is reported as 7 ("III + III") on the source document and "4" on the CRF. The left pulmonary vein further ablation time (minutes) is reported as "1" on the source document and as "6" on the CRF.
4. **You failed to disclose to the sponsor sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements required under part 54, and you failed to promptly update this information if any relevant changes occurred during the course of the investigation [21 CFR 812.110(d)].**

You failed to adhere to the above stated regulation. On March 10, 2006, you sent a letter to the [redacted] in which you stated that you have [redacted] stock options with AtriCure; that you are a scientific advisor and consultant to [redacted] and that you received [redacted] to [redacted] per month in 2005 as a scientific advisor to AtriCure and [redacted] - [redacted] in 2005 as compensation for training and proctoring. You also signed a royalty agreement with [redacted] effective October 1, 2005, for payments of at least [redacted] per quarter, for [redacted] use of the "[redacted]." We are also aware that you received payments from [redacted] of at least [redacted] in 2002; [redacted] in 2003; [redacted] in 2004; [redacted] in 2005; and [redacted] in 2006.

This information is in direct conflict with two "Conflict of Interest Statements" you signed in 2005:

- A statement signed by you on 6/27/05 stated that you were not a scientific advisor or consultant to [redacted] that you did not receive an honoraria exceeding [redacted] annually;

that you did not own any stock options with the company; and that the study sponsor did not hold patent rights to inventions created by you.

- A statement signed by you on 9/7/05 stated that, although you were a scientific advisor or consultant to [redacted] and did receive an honoraria exceeding [redacted] annually, you did not have stock options with the company, and that the study sponsor did not hold patent rights to inventions created by you.

A June 19, 2006, response made on your behalf by [redacted], Acting Compliance Officer (Research) for the [redacted] included a detailed description of the actions taken by the [redacted] and the IRB regarding conflict of interest issues that arose regarding financial relationships between you and [redacted] the sponsor of the [redacted] study and the manufacturer of the device for your [redacted] investigator-initiated study. The corrective actions described in the letter appear to be appropriate to address the issues of conflict of interest and inaccurate financial disclosure statements, and to prevent recurrence of similar problems in the future.

One corrective action noted in the letter from [redacted] stated that the IRB required, "All patients enrolled in both Studies to be informed of the conflict and asked to sign a revised informed consent document signifying their willingness to continue in the studies." The letter from the IRB, dated March 31, 2006, noted that, "All previously enrolled subjects must be re-consented with the revised consents [redacted], dated [redacted] within 30 days of the date of the letter. Please provide us with a list for each study that details the date each subject has been "re-consented" with the revised consent form.

5. You failed to adequately supervise the conduct of the study [21 CFR 812.110(c)].

Regarding the [redacted] study, you failed to adhere to the above-stated regulation, and you failed to adhere to the Clinical Study Agreement you signed on October 25, 2005. Specifically, as the principal investigator for this study until 3/17/06, you failed to review and sign completed CRFs as required by the study protocol. In fact, you informed the FDA investigators that you did not review the CRFs and did not have access to the electronic CRF database. At the close of the FDA inspection, you read a statement to the FDA investigators and provided a signed copy of the statement in which you said, "I am not, nor ever have been involved with any data collection or entry in any study. If my life depended on it, I could not access data. I do not know how. I do not know which patients are enrolled in the current FDA study."

You provided three separate written responses through other parties to the violations discussed during the FDA inspection.

- A July 10, 2006, response from your attorneys of record, [redacted] and [redacted], of [redacted] notes that "Dr. Wolf recognizes and understands that, as Principal Investigator, the Inspectional Observations made by the FDA Investigators and other auditors are his responsibility," and that "responsibilities as Principal Investigator extended beyond simply referring potential study subjects to the research study coordinator." The response also included a letter to you, dated 7/5/06, from [redacted] Dean of the [redacted] [redacted] noted that "you and your research team have inadequate training in clinical research and that one trial was performed in a sloppy, careless, and inconsistent manner." He further recommends that you

and your research staff “promptly make arrangements to receive appropriate, thorough training in clinical research.” Please provide us with documentation of the clinical research training that has been or will be undertaken, including the names and titles of all study personnel, a description of the training, and dates that such training has been or will be completed.

- A July 28, 2006, letter from [redacted] and [redacted], of [redacted] and [redacted] included a document titled “Randall K. Wolf, MD – Standard Operating Procedures as Investigator in Clinical Trials.” This document details a number of promises made in your name regarding the conduct of clinical trials. This response is not acceptable, because this document is not dated and not signed by you. We have no evidence that you agree with the promises made in this document, or that you have even reviewed the document. Please provide us with a signed and dated copy of the “Standard Operating Procedures as Investigator in Clinical Trials” or a statement signed and dated by you in which you agree to the promises made in the document.
- The June 19, 2006, response from [redacted] also included a number of new SOPs adopted by the Department of [redacted] regarding human subject research. The letter noted that training on these SOPs will be provided this summer. Please provide us with documentation that all personnel involved in the two studies discussed in this letter have been appropriately trained on these SOPs.

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.

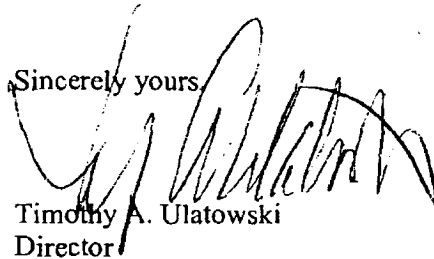
You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at <http://www.fda.gov/oc/ohrt/irbs/>. Any submitted corrective action 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 the FDA Cincinnati District Office, 6751 Steger Drive, Cincinnati, OH 45237. Please send a copy of your response 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,

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

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