Inspections, Compliance, Enforcement, and Criminal Investigations

Advanced Interventional Pain Ctr IRB 2/7/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

February 7, 2014

WARNING LETTER

VIA UNITED PARCEL SERVICE

Pattanam Srinivasan, MD
Head Official of Advanced Interventional Pain Center IRB
3554 Promenade Parkway, Suite H
Lafayette, IN 47909

Dear Dr. Srinivasan:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection of your Institutional Review Board (IRB) from September 30, 2013, to October 24, 2013, by an investigator from the FDA Detroit District Office. This correspondence addresses your role as the head official of the Advanced Interventional Pain Center Institutional Review Board (IRB) that oversaw your investigation. In addition, we note that you are both sponsor and Clinica Investigator (CI) of the study entitled, "**(b)(4)**". A separate correspondence will address the inspection findings of the sponsor and CI. Please note that we have concerns about you serving in these distinct roles simultaneously.

This inspection was conducted to determine whether your IRB is in compliance with applicable federal regulations. IRBs that review investigations of devices must comply with applicable provisions of Title 21, Code of Federal Regulations (CFR) Part 56-Institutional Review Boards, Part 50-Protection of Humai Subjects, and Part 812-Investigational Device Exemptions. This letter also requests prompt corrective action to address the violations cited and discusses your written response dated November 11, 2013, tc the noted violations**.**

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions, Premarket Approval applications, and Premarket Notification submissions 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 serious violations of 21 CFR Part 50 - Protection of Human Subjects and Part 56- Institutional Review Boards, which concerns

requirements prescribed under section 520(g) of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. § 360j(g). At the close of the inspection, the FDA investigator presented inspectional observations Form FDA 483 for your review and discussed the observations listed on the form with you. The deviations noted on the Form FDA 483, your IRB's written response, and our subsequent review of the inspection report, are discussed below:

1. Failure to have adequate written procedures governing the functions and operations of the IRB. [21 CFR 56.115(a)(6)]

An IRB is required to prepare and maintain adequate written procedures. But your IRB's procedure manual: "Advanced Interventional Pain Center Institutional Review Board Policies and Procedures," dated 2009-2011, lacked written procedures for the following IRB activities:

- conducting initial and continuing review of research
- ensuring that changes in approved research, after IRB approval had already been given, would not be initiated without IRB review and approval
- determining which projects require review more often than annually and need verification from sources other than the investigator that no material changes have occurred since previous IRB review
- ensuring prompt reporting to the IRB of changes in research activity

It is critical that your IRB prepare and maintain adequate written procedures for the review of research These procedures will help to ensure that research is reviewed in a timely manner and that the findings are adequately reported to the institution and the clinical investigator. Your IRB's lack of written procedures for the review of research can compromise the rights, safety, and welfare of research subjects and decrease the integrity and validity of research data.

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

An IRB is required to ensure that information given to subjects as part of informed consent is provided in accordance with 21 CFR 50.25. This includes information that would meaningfully add to the protection of the rights and welfare of human subjects.

Your IRB approved an informed consent document (ICD) for the study entitled, "**(b)(4)**". The ICD did not include the required information in accordance with 21 CFR 50.25:

- the purpose of research
- the expected duration of the subject's participation
- a description of the procedures to be followed
- identification of any procedures that were experimental

Without this important information, the study subjects would not be able to correctly weigh the risks and benefits of enrolling in the study. As a result they would not have enough information to make an informed decision on whether to participate in the research study.

3. Failure to ensure that no IRB member participated in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. [56.107(e)]

To approve research, an IRB must ensure that voting members do not have a conflict of interest in the research. The IRB failed to ensure that IRB members with conflicting interests in the project being reviewed did not participate. An example is the following:

- The IRB provided a DVD documenting subjects' interviews before and after treatment with the device. The DVD shows Dr. Turner, IRB Chairman and voting member, performing study procedures for "**(b)(4)**," on a patient on **((b)(4); (b)(6))**. Dr. Turner voted on the study during an IRB meeting held on 10/18/2011.

In order to ensure that your IRB's review of research is fair and equitable it is essential to confirm that any member who may have a conflict of interest does not participate in your IRB's review of future research studies.

4. Failure to prepare and maintain adequate documentation of IRB activities. [21 CFR 56.115(a)(1), (a)(2), and (a)(4)]

To fulfill the requirements of this regulation, an IRB shall prepare and maintain adequate documentatio of IRB activities, including the following: copies of all research proposals reviewed, minutes of IRB meetings, and copies of all correspondence between the IRB and the investigators. You failed to maintain the following:

- copies of the original protocol that was reviewed during the convened IRB meeting held on 11/11/2009
- meeting minutes in sufficient detail to show the votes on actions including the members voting for against, and abstaining, for convened IRB meetings held on 11/11/2009 and 10/18/2011
- documentation of a discussion held between the IRB Chairman and the Clinical Investigator pertaining to the closing of the study

It is critical that your IRB prepare and maintain adequate written procedures in order to ensure that the rights and welfare of study subjects are protected.

Your IRB's written response did not state the following:

- how or when the newly written procedures will be implemented,
- who would provide training to the IRB members,
- what documentation will be provided notifying the FDA that IRB members were trained,
- how and who will re-consent the patients that previously participated in the study and how the FDA will be informed of the re-consenting, and
- how the IRB will review future informed consent documents ensuring that all elements of consent are included.

In addition, your newly-written procedures are not written in sufficient detail to address the specific points stated in 21 CFR 56.108 (a) and (b). The new procedures for Voting at IRB Meetings; Changes ir Research Activity; Reporting Requirements; and the Communications Between Investigators, IRB, and IRB Members, do not address the regulations. Also, the revised procedures do not address the determination of which projects require review more often than annually and need verification from sources other than the investigators that no material changes have occurred since previous IRB reviews [21 CFR 56.108(a)(3)].

We also note that the newly-written procedures do not address email voting activities for protocol changes that are more than minor in nature. For example, **(b)(4)** out of **(b)(4)** board members concurred via email in response to a notification sent directly by the clinical investigator on 1/10/2012. Your IRB approved changes to the protocol that added **(b)(4)** subjects receiving **(b)(4)** treatment via email correspondence with the board members, which was neither deliberated nor voted upon at a convened meeting.

The violations described above are not intended to be an all-inclusive list of problems that may exist at the IRB. The IRB is responsible for ensuring compliance with the Act and applicable regulations.

We believe that a teleconference is necessary to further discuss the Form FDA 483 observations and any corrective actions you have taken or plan to implement. Please contact Ms. Veronica Calvin at the address below within two weeks of receiving this letter to propose several dates and times for this teleconference.

Also, within 15 working days of receiving this letter, please provide documentation of the actions that you have taken or will take to correct these violations, to prevent the recurrence of similar violations, and a plan to monitor the effectiveness of your corrective actions. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you.

Your response should reference "CTS # EC130356/E001" and be sent to:

Attention: Veronica Calvin
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
10903 New Hampshire Avenue
Building 66, Room 3508
Silver Spring, Maryland 20993-0002.

A copy of this letter has been sent to FDA's Detroit District Office, 300 River Place, Suite 5900, Detroit, MI 48207. Please send a copy of your response to that office.

The Division of Bioresearch Monitoring has developed introductory training modules in FDA-regulated device clinical research practices, which are available on the FDA website. The modules are for persons involved in FDA-regulated device clinical research activities. These modules are located at the following website address: http://www.fda.gov/Training/CDRHLearn/ucm162015.htm[1].

If you have any questions, please contact Veronica Calvin at 301-796-5647 or via email at Veronica.Calvin@fda.hhs.gov.

Sincerely yours,
/S/
Steven D. Silverman
Director
Office of Compliance
Center for Devices and
Radiological Health

cc:
R. Charles Turner, M.D.
IRB Chairman
3554 Promenade Parkway, Suite H
Lafayette, IN 47909

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Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

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Ph. 1-888-INFO-FDA (1-888-463-6332)
Contact FDA

Links on this page:

1. http://www.fda.gov/Training/CDRHLearn/ucm162015.htm