Inspections, Compliance, Enforcement, and Criminal Investigations

Michael Ring, MD 1/14/13

Department of Health and Human Services

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

JAN 14 2013

WARNING LETTER

VIA UNITED PARCEL SERVICE

Michael E. Ring, MD
Providence Spokane Heart Institute
122 W 7th Avenue
Suite 450
Spokane, WA 99204-2349

Dear Dr. Ring:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection of your clinical site from July 24, 2012, to August 23, 2012 by investigators from the FDA Seattle District Office. This inspection was conducted to determine whether activities and procedures related to your participation in the clinical study, "Medtronic CoreValve U.S. Pivotal Trial," Investigational Device Exemption (IDE) G100012, complied with applicable federal regulations. The Medtronic CoreValveis 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), because it is intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or to affect the structure or function of the body. This letter requests prompt corrective action to address the violations cited and discusses your written response dated September 14, 2012, to the noted violations.

The inspection was conducted under a program designed to ensure that data and information contained in requests for IDEs, 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 Title 21, Code of Federal Regulations (CFR) Part 812 - Investigational Device Exemptions and Part 50 - Protection of Human Subjects, which concern requirements prescribed under section 520(g) of the Act, 21 U.S.C. § 360j(g). At the close of the inspection, the FDA investigator presented an 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 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 50.25(a)(1)-(2), 21 CFR 50.20, 21 CFR 50.27(a), and 21 CFR 812.100]

As a clinical investigator, you are responsible for ensuring that informed consent is obtained in accordance with 21 CFR Part 50. Pursuant to 21 CFR 50.20, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. You failed to adhere to the above-stated regulations. Examples of these failures include, but are not limited to the following:

a. You allowed some subjects to undergo invasive, research-specific screening tests, such as CT angiogram, before they signed the screening informed consent document (ICD). For example:

- **(b)(6)** underwent the CT angiogram screening test on May 9, 2011, and signed the screening ICD on May 10, 2011, one day after the test.
- **(b)(6)** underwent the CT angiogram screening test on March 15, 2012, but did not sign the screening ICD.

CT angiography carries the risk of contrast-induced kidney disease, allergic reaction, and radiation exposure. You must obtain and document informed consent from subjects before conducting any research-related procedures to confirm that the subjects are aware of and accept the associated risks.

Your response to this observation appears to be adequate. You stated that you have a revised Standard Operating Procedure (SOP) that includes a checklist item to ensure that consent is obtained prior to any study-related procedures being performed and that study personnel will be re-trained on this SOP by September 28, 2012.

b. You allowed some subjects to be randomized before they signed the procedure ICD. For example:

- **(b)(6)** was randomized on August 10, 2011, and signed the procedure ICD on September 2, 2011, more than three weeks after randomization.
- **(b)(6)** was randomized on October 28, 2011, and signed the procedure ICD on November 1, 2011, four days after randomization.
- **(b)(6)** was randomized on November 11, 2011, and signed the procedure ICD on January 17, 2012, more than two months after randomization.

The randomization was done before the subjects were apprised of all possible study procedures and their associated risks. You must obtain and document informed consent from the subjects prior to randomization to confirm that the subjects are aware that they may be chosen to have transcatheter aortic valve replacement or surgical aortic valve replacement (SAVR) and the risks associated with these procedures.

Your response is inadequate because, although you state that you will create a unified ICD that will explicitly state that high-risk patients will be randomized and receive either the CoreValve device or a standard, commercially-available surgical aortic valve replacement, which does not involve an experimental device, you do not explain how you will ensure that you will obtain informed consent prior to randomization.

2. Failure to ensure that 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 an IRB or FDA, and failure to notify the sponsor and reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency within 5 working days after the emergency occurred. [21 CFR 812.100, 21 CFR 812.110(b), 21 CFR 812.150(a)(4)]

As a clinical investigator, it is your responsibility to conduct the investigation in accordance with the signed agreement with the sponsor, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by an Institutional Review Board (IRB) or FDA. (See 21 CFR 812.100 and 21 CFR 812.110(b)). It is also your responsibility, as a clinical investigator, to notify the sponsor and the reviewing IRB, within five working days, of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. (See 21 CFR 812.150(a)(4)). You failed to adhere to the above–stated regulations. Examples of these failures include, but are not limited to the following:

a. You failed to notify the sponsor and the reviewing IRB within five working days of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, as required by 21 CFR 812.150(a)(4) and the study protocol. For example:

- **(b)(6)** underwent SAVR and two emergency procedures that were not part of the investigational plan: tricuspid annuloplasty due to severe tricuspid regurgitation and emergency single vessel revision of an existing coronary artery bypass graft (CABG). Although the emergency deviation from the investigational plan occurred on June 29, 2012, it was not reported to the sponsor and IRB until August 8, 2012, far more than five working days after the deviation occurred.
- **(b)(6)** underwent an emergency single vessel CABG during the study procedure on October 5, 2011. There is no record of any report of the protocol deviation to the sponsor and IRB.

Lack of reporting of emergency procedures that deviate from the protocol can have general safety implications for the study.

Your response is inadequate. Although you state that you will implement a study–site work practice for tracking all study patients in which the study coordinator will come to the operating room before the end of every surgery and meet with the investigator to determine whether any protocol deviations occurred during surgery, you failed to describe how you will ensure that protocol deviations are reported.

b. The IRB approval letter states that "[e]mergent problems, unexpected side effects, serious adverse reactions and deaths, whether or not project-related are to be reported within five days." You failed to report the following two deaths to the IRB within the five day timeframe required by the IRB:

- **(b)(6)** died April 28, 2011. You did not report the death to the IRB until October 21, 2011.
- **(b)(6)** died May 11, 2011. You did not report the death to the IRB until October 21, 2011.

Lack of reporting of deaths for all enrolled subjects, even those who have not undergone the experimental procedure, can make the data unreliable.

Your response to this observation appears to be adequate. You stated that you will notify the IRB within 5 days of becoming aware of the death of a subject or adverse event suffered by a subject who signed a unified informed consent document and that you will retrain study staff on reporting deaths.

3. Failure to maintain accurate, complete, and current records relating to the investigation. [21 CFR 812.140(a)(1), (3), and (4)]

As an investigator, you are responsible for maintaining accurate, complete, and currentrecords relating to the investigation. (See 21 CFR 812.140(a)). You failed to adhere to the above-stated regulations. Examples of these failures include, but are not limited to the following:

a. **(b)(6)**
- The Electronic Case Report Form (eCRF) lacks baseline vital signs, permanent pacemaker) interrogation findings, or laboratory values.
- The post-procedure electrocardiogram and interpretation notes are missing from the study chart.
- The investigator did not sign the Screening Transthoracic Echocardiogram Interpretation source document, baseline visit assessment worksheet, or the discharge worksheet.

b. **(b)(6)**
- The investigator did not sign the NIH Stroke Scale assessment, the baseline assessment worksheet, or the discharge worksheet.
- Part of the original screening worksheet is missing and the two copies that exist differ regarding exclusion criteria for mitral or tricuspid regurgitation and mitral stenosis.

The missing data include clinically significant information regarding case histories, test results, clinical assessments, and follow-up visits. This information is required to ensure that subjects are receiving the necessary study procedures and are not experiencing medical complications that may be device related. Accurate, complete, and current research records also help ensure the validity of the data collected from your site. The failure to maintain accurate, complete and current records relating to the investigation may undermine the validity of the data and lead to errors in subject management with potentially serious health consequences.

Your response included a commitment from the hospital to ensure that sufficient resources are available and devoted to the tasks of timely completion of eCRFs and charts. You also stated that you have reiterated to the study staff the need to prioritize data entry and that staff will be retrained on the need to request additional resources when needed to perform recordkeeping functions in a timely manner. Your response is inadequate because you have not assessed how your failure to keep accurate, current, and complete records relating to the investigation occurred and what actions, in addition to additional resources, are needed to prevent recurrence.

Additionally, the following two items were discussed during the close of the inspection. It is important that you also correct these deficiencies.

- Records of monitoring reports were not complete or current, as required by 21 CFR 812.140 (a)(1). Specifically, the FDA field investigator observed that there were no reports for monitoring visits that occurred May 1-3, 2012, May 22-24, 2012, and June 20-28, 2012.

Review and maintenance of monitoring reports help you ensure your site is following the investigational plan.

- Failure to maintain accurate, complete, and current records of the research protocols, as required by 21 CFR 812.140(a)(4). Specifically, the FDA field investigator observed that ER protocol V. 9.0 and HR protocol V. 7.0 and 8.0 were not on file at the site.

It is important for you to maintain all versions of the protocol at your site and have them readily available for review by you and your staff. This helps ensure subject safety by allowing for prompt review of the protocol to confirm that the study is conducted according to the investigational plan. This also helps you to promptly recognize any protocol deviations and report them to the sponsor without delay.

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.

In addition, your recruitment letter to potential referring physicians was not approved by the IRB. Although the IRB approval did not specify that recruitment materials must be approved prior to use, we suggest that you provide these kinds of materials to your IRB prior to use whenever possible.

Within 15 working days of receiving this letter, please provide documentation of theadditional actions that you have taken or will take to correct these violations and to prevent the recurrence of similar violations in current or future studies for which you are the clinical investigator. Although the study is closed to enrollment, it is your responsibility to correct these deficiencies and prevent their recurrence for the duration of the study and in any future clinical research that you conduct. Your response to this letter should describe your corrective and preventative action plan, and include copies of any written SOPs that you implement. Your corrective action plan should include projected completion dates for each action to be accomplished and a plan for monitoring the effectiveness of your corrective actions. Please also include a documented training plan listing each staff member by name and position, and the SOP they will be trained on. Additionally, please provide a log that documents completion of training by staff and documentation that you have completed training in good clinical practices in the conduct of human subject research.

Also, please provide a complete list of all FDA–regulated device clinical research in which you have participated for the last five years, including the name of the study and test article, the name of the sponsor, the number of subjects enrolled, and the current status of the study.

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.

Your response should reference CTS G100012/E001 and be sent to:

Attention: Anne T. Hawthorn
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
10903 New Hampshire Avenue
Building 66, Room 3504
Silver Spring, Maryland 20993-0002.

A copy of this letter has been sent to FDA's Seattle District Office,22215 26th Ave SE, Suite 210, Bothell, WA 98021-4421. Please send a copy of your response to that office.

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/[1].

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.

If you have any questions, please contact Anne Hawthorn at (301) 796-6561 or anne.hawthorn@fda.hhs.gov.

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

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

Links on this page:

1. http://www.fda.gov/oc/ohrt/irbs/