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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

JAN 9 2008

Food and Drug Administration
Center for Devices and
Radiological Health
9200 Corporate Blvd
Rockville, MD 20850

WARNING LETTER

VIA FEDERAL EXPRESS

Ansaar T. Rai, M.D.
West Virginia University
Department of Radiology
Room 2278
1 Stadium Drive
Morgantown, WV 26506-9235

Dear Dr. Rai:

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 June 25 through June 29, 2007, by an investigator from the FDA Baltimore District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study [redacted]

[redacted] complied with applicable federal regulations. The [redacted] 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 response 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 applications (PMA), 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 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, 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 obtain informed consent signed and dated by the subject or the subject's legally authorized representative at the time of consent [21 CFR 50.27(a) and 812.100].

Pursuant to the above stated regulations, clinical investigators are responsible for obtaining consent using an IRB approved consent document prior to any study related procedures and for ensuring that informed consent is documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. Examples of your failure to adhere to the above stated regulation include but are not limited to the following:

The informed consent form (ICF) for subject [] was not dated by the subject or the subject's representative. Jeff Carpenter, co-investigator, signed and dated the ICF on 11/3/06. The Device Log Sheet documents that [] components were used on subject []

In your October 26, 2007, response you state that you did obtain an informed consent for subject [] a copy of which is attached to your response. You also attach a signed and dated Health Insurance Portability and Accountability Act (HIPAA) authorization to your response. However, your response is inadequate because the ICF was not dated by the subject or the subject's representative at the time of consent, and the HIPAA authorization is separate from and does not fulfill informed consent requirements. Please provide the corrective and preventive actions you have taken or plan to take to prevent this violation in the future.

2. Failure to prepare and submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation no event later than 10 working days after the investigator first learns of the effect [21 CFR 812.150(a)(1)].

Pursuant to the above stated regulation, clinical investigators are responsible for preparing and submitting to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect (UADE) occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. Examples of your failure to adhere to the above stated regulation include but are not limited to the following:

- Subject [] experienced a small [] on [] and a urinary tract infection with positive blood cultures on [] You failed to report these UADEs to the sponsor or to the IRB within the specified time period.
- Subject [] was admitted on [], suffered respiratory failure on [] and expired on [] There is no documentation that the sponsor was notified of this UADE.

Your response states that you reported [redacted] to the IRB on [redacted] and includes a copy of the "Problem Reporting Form" that you submitted. Your response is inadequate in that it does not address your failure to report this UADE to the sponsor or your failure to report the UADEs for subject [redacted] to the sponsor or to the IRB. As stated above, please provide the corrective and preventive actions you have taken or plan to take to prevent this violation in the future.

3. Failure to ensure control of devices and failure to conduct the investigation according to the signed agreement and the investigational plan [21 CFR 812.100 and 812.110(b)].

Pursuant to the above stated regulations, clinical investigators are responsible for ensuring control of devices and for conducting the investigation according to the signed agreement and investigational plan. Examples of your failure to adhere to the above stated regulation include but are not limited to the following:

- The protocol states that the investigator shall store the investigational devices in a secure location with limited access to prevent non-study subjects from receiving the device. However, you stored the investigational devices with the Interventional Radiology general inventory, which is not secure.
- The protocol states that the investigator shall maintain records pertaining to device inventory, including date of receipt, lot number, and disposition of each device including patient number. You failed to follow the protocol in that the device log sheet lacks patient numbers for subject [redacted]. Case report forms (CRF) for subject [redacted] documented the use of components # [redacted] and # [redacted] however, there is no patient ID associated with those devices on the Device Log Sheet.

Your response to the above violations states that the failure to maintain control of devices or follow the protocol was an oversight on your part and that since undergoing training you realize that one of your responsibilities as clinical investigator is assuring that devices are maintained and accounted for in accordance with the protocol. Your response is inadequate in that it does not provide specific steps you have taken or intend to take, other than your training, to prevent these deviations from occurring in future studies. Please provide the corrective and preventive actions you have taken or plan to take to prevent this violation in the future.

- The protocol states that pre-treatment (admission) evaluations include liver enzymes, international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT), that immediate post-procedure evaluations include INR/PT/PTT, and that [redacted] post procedure evaluations include liver enzymes (aspartate aminotransferase (AST) and alanine transaminase (ALT)), INR/PT/PTT, and lipid profile. However, you failed to perform the following evaluations:

- For subject []:
 - You failed to perform admission liver enzyme testing
 - You failed to perform post-procedure INR coagulation study
- For subject []:
 - You failed to perform admission liver enzyme testing
 - You failed to perform [] post-procedure PT and PTT testing
- For subject []:
 - You failed to perform admission liver enzyme tests and INR
 - You failed to perform [] post-procedure lipid profile
- The protocol states that investigators will report all serious adverse events and serious adverse device effects (collectively, SAEs) to the sponsor no later than [] after occurrence, and that all SAEs must be documented on the Serious Adverse Events form, which must be completed, signed, and sent by fax or overnight courier to the sponsor within [] working days. You failed to follow the protocol in that you did not complete the Serious Adverse Events forms for subject [] and that you failed to notify the sponsor of the SAEs suffered by subject [] and subject [] within the specified time frame.

Your response states that you reported the SAE regarding subject [] to the IRB on [] and attaches this report. Your response is inadequate in that it does not address your failure to document the SAEs suffered by subject [] on the SAE form or your failure to report the SAEs suffered by subject [] and subject [] to the sponsor. Please provide the corrective and preventive actions you have taken or plan to take to prevent this violation in the future.

- The protocol states that the investigator and study staff shall complete CRFs and that it is the investigator's responsibility to ensure the quality of the data collected and recorded. You failed to follow the protocol in that CRFs were incomplete for at least [] of the [] subjects enrolled in your study. Specifically, subject identification is missing from CRFs for subjects [], [], and [].

Your reply states that you have undergone training regarding investigator responsibilities and good clinical practices and attaches a certificate of completion. Please indicate the dates of training and the topics covered as it is unclear whether the training included specific information regarding your responsibility as a clinical investigator. In addition, your response is inadequate in that, other than training, you have not indicated any corrective or preventive action that you have taken or plan to take to prevent recurrence of the above violations. Please provide the corrective and preventive actions you have taken or plan to take to prevent this violation in the future.

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

Pursuant to the above stated regulation, clinical investigators are responsible for maintaining accurate and complete records relating to each subject's case history and exposure to the device. Examples of your failure to adhere to the above stated regulation include but are not limited to the following:

- For subject []:
 - You failed to complete the CRF "Study Completion Status" page and you failed to sign and date the CRF "Investigator's Statement of Verification" page.
 - CRFs lack subject identification on 20 pages.
 - There are discrepancies between the CRFs and the sponsor's electronic device lot sheet: the CRFs document the lot numbers of [] while the device lot sheet documents the lot number of only []
- For subject []:
 - CRFs lack subject identification on four pages.
 - There are discrepancies between the CRFs and the sponsor's electronic device lot sheet: the CRFs document the lot numbers of [] while the device lot sheet documents the lot number of only []
- For subject []: CRFs lack subject identification on one page.

Your response states that your failure to complete the CRFs was due to your lack of training regarding your responsibilities and explains that you have undergone training to remedy this. As discussed above, your response is inadequate in that it is unclear whether the training included specific information regarding your responsibility as a clinical investigator. Please provide the corrective and preventive actions you have taken or plan to take to prevent this violation in the future.

Your response to Form FDA 483 Observation 1, Item 3, states that you have hired a new study coordinator and arranged for training of potential co-investigators. This should assist you in preventing some of the above violations. In addition, we note that your response states that all future device trials will be managed by the Clinical Trial Research Unit (CTRU), which "has the infrastructure, support, and trained and certified staff whose sole job is to conduct clinical trials. We will not run any clinical trials from our department (Radiology) which lacks the resources to satisfactorily manage device trials." It is unclear whether this means that you will no longer be participating as a clinical investigator in clinical trials. Please clarify this statement. Please be aware that clinical investigators are responsible for the conduct of clinical trials and cannot delegate these responsibilities.

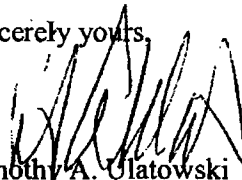
The violations described above are not intended to be an all inclusive list of problems that may exist with your clinical study. It is your responsibility as a clinical investigator to ensure compliance with the Act and applicable regulations.

Within fifteen (15) working days of receiving this letter, please provide written documentation of the additional 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. In addition, please provide a complete list of all clinical trials 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 actions could result in 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. Send your response to: Attention: Doreen Kezer, MSN, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 9200 Corporate Boulevard, HFZ-311, Rockville, Maryland 20850.

A copy of this letter has been sent to the Baltimore District Office, 6000 Metro Drive, Suite 101, Baltimore, Maryland 21215-3215. Please send a copy of your response to that office. If you have any questions, please contact Ms. Doreen Kezer by telephone at (240) 276-0125 or via e-mail at doreen.kezer@fda.hhs.gov.

Sincerely yours,



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