DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

April 11, 2013

VIA UNITED PARCEL SERVICE

James F. McGuckin, Jr., M.D.
Chief Operating Officer, Principal Investigator
1450 Parkside Avenue, Unit 18
Trenton, NJ 08638

Dear Dr. McGuckin:

The purpose of this letter is to inform you of the findings of a Food and Drug Administration (FDA) inspection of your clinical site from July 2, 2012, to July 20, 2012, by investigators from the FDA New Jersey District Office. This inspection was conducted to determine whether activities and procedures related to your participation in the clinical study titled, "Multi-center Registry of Chronic Cerebrospinal Insufficiency Testing and Treatment," (the Hubbard Protocol) complied with applicable federal regulations. The catheters and stents used in this study are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(h), because they are 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.

The clinical study is an investigation of a significant risk device, which means FDA approval of an application for Investigational Device Exemption (IDE) is required prior to commencement of the study. At the time you conducted the investigation and as of the day this letter was signed, the study sponsor, the Hubbard Foundation, had yet to obtain IDE approval from FDA, in violation of section 520(g) of the Act, 21 U.S.C. § 360j(g) and 21 CFR 812.20 and 812.42.

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 several violations of Title 21, Code of Federal Regulations (CFR) Part 812 -

Investigational Device Exemptions, and Part 50 - Protection of Human Subjects, which concerns 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 review and discussed the observations listed the form with Laurie Brown, RN BSN (Study Coordinator and Director of Clinic Compliance), and Cynthia Gould, RN BSN (Center Manager). The deviations noted on the Form FDA 483, your written response dated August 9, 2012, and our review of the inspection report, are discussed below. Although you stated in your August 9, 2012, response that you immediately discontinued any further involvement with the Hubbard Foundation after FDA's inspection, we have the following concerns with your response to the Form FDA 483, particularly because your response alludes to participation in future studies. It is imperative that these issues be corrected should you choose to be involved in this or another clinical study of a device in the future.

1. **Failure to conduct the investigation according to signed agreement, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by an Institutional Review Board (IRB) or FDA. [21 CFR 812.100, 21 CFR 812.110(b)].**

An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations. In addition, an investigator is responsible for ensuring that an investigation is conducting according to any conditions of approval imposed by the IRB or FDA. The inspection conducted at your site revealed several instances where you did not adhere to this responsibility. This failure can compromise the reliability of the data from the study. The safety of human subjects participating in the study may also be affected resulting in increased risk of harm to them. Examples of this failure include, but are not limited to, the following:

You did not obtain creatinine values to evaluate the kidney function for at least 14 subjects, as stated on the case report forms. Abnormal kidney function is a study exclusion criteria set forth in the protocol. Subjects with abnormal creatinine values and probable abnormal kidney function may have been improperly enrolled in the study. As a result, these subjects would be at increased risk of developing worsening kidney disease or kidney failure.

a. You did not obtain Magnetic Resonance Imaging (MRI) testing at 6 months for at least 11 subjects as stipulated in the protocol. This compromised the safety of study subjects because timely MRI testing and follow up can help mitigate certain risks such as hemorrhage and vascular

restenosis associated with the study. To ensure subject safety, important diagnostic tests like MRI should be performed according to the protocol.

b. You did not report serious adverse events, which your staff identified as severe, for three subjects: worsening symptoms of depression (subject 1001), fatigue and pressure in the back of the head (subject 1009), and allergic reaction (subject 1121040). The Investigator Statement of Agreement with BioMed IRB and the IRB approval letter, dated March 30, 2011, required reporting serious adverse events occurring at your site within 10 calendar days from the date of discovery by the investigator. Reporting adverse events to the IRB is important for ensuring the safety and welfare of study subjects. These symptoms are clinically significant as they may represent worsening disease or a new medical condition. The IRB should be aware of this information as it helps it evaluate and decide whether changes need to be made to the study to ensure subject safety.

c. You did not file significant protocol deviations with the IRB, for significant protocol deviations described in items a-c above, as required by the Investigator Statement of Agreement with BioMed IRB. Protocol deviations reports are important components of the study that are also needed to ensure subject safety. They should be filed with the IRB in a timely manner so that they can be reviewed and appropriate action taken, if needed.

d. You did not report the June 30, 2011, clinical site closures for the Jersey City and Piscataway, New Jersey, sites to the IRB as instructed by the IRB's site approval letter, dated March 30 2011. According to the continual approval notification, dated April 4, 2012, these sites were still active in 2012.

e. You used recruitment materials not approved by the IRB. The IRB requirements were stipulated in the Investigator Statement of Agreement with BioMed IRB and the IRB approval letter, dated March 30, 2011. Your failure to secure IRB approval of recruitment materials prevented the IRB from ensuring that the rights and welfare of study subjects are protected.

Adherence to the investigational plan, signed investigator agreement, FDA regulations, and IRB conditions helps ensure that research subjects will not be exposed to known hazards that would place them in jeopardy or invalidate the outcome of the research. Your adherence to the investigational plan, investigator agreement, and IRB approval requirements in future studies is important to minimize unnecessary risks to subjects. Adherence to these requirements is particularly important in studies such as this, which involve invasive procedures and a high risk study population with an unpredictable course of disease.

We acknowledge that, in your August 9, 2012, response you stated that you discontinued any further involvement with the Hubbard Foundation. Nevertheless, we have particular concerns about your responses and corrective actions, which pertain to the research subjects you treated under the Hubbard Protocol as well as future studies in which you may choose to participate. Specifically, in your written response, you acknowledge the deficiencies noted above and indicate that you have created a Clinical Research Manual to apply to all future studies in which Vascular Access Centers personnel participate. Also, you submitted a check-off sheet signed by site staff to evidence that they have read and understand the new procedures. Section H4dl of your new manual titled, "The Protection of Human Subjects in Research," states that clinical laboratory testing will be performed within industry standard. We have concerns about this response since clinical research must follow the protocol, investigational plan, and requirements of the reviewing IRB.

In addition, Section B of the Clinical Research Manual describes educating research staff, but does not give sufficient detail about the training process or its timing; when hiring new staff, in particular. Moreover, your response does not address how the new manual will prevent the issues identified above from recurring.

We are also concerned that, while Section 12.A of your Clinical Research Manual indicates that you will require IRB review of your promotional materials, it does not specify that promotional materials must be approved by the IRB before use.

2. Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50. [21 CFR 812.100; 21 CFR 50.25(a)(1) and (5)]

As an investigator, you are responsible for protecting the rights, safety, and welfare of subjects under your care by ensuring informed consent is obtained in accordance with 21 CFR Parts 50. You failed to ensure that informed consent was obtained from subjects and documented in accordance with these regulations. Specifically, you used informed consent documents that did not include the duration of subject participation or notice that FDA may inspect the records.

A valid informed consent process ensures that before research subjects decide to participate they have a clear understanding of the length of their participation and who may review or inspect their study records. Although you submitted a corrected informed consent document, you did not provide a training plan that addresses how you will implement revised procedures with your staff.

Page 5 – James F. McGuckin, Jr., M.D.

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. We will verify your corrective actions, in particular your assertion that you are no longer conducting clinical studies, during our next inspection.

We request that you identify all subjects who participated in the clinical protocol supplied by the Hubbard Foundation. Please also provide us with a copy of the IRB-approved letter that informed subjects that the study referenced in this letter has been closed. The letter should have included any pertinent information that was missing from the informed consent document (i.e., the duration of subject participation and a notice that FDA may inspect the records).

In addition, before engaging in any clinical studies in the future, please describe how your new manual will ensure that the training process is adequate and that any new staff will be trained as they are hired. Provide FDA confirmation of training in human subject research for yourself and your research staff. For example, this may be accomplished by providing completed training certificates that include the title of the training, the staff members trained, and date completed. In addition, please correct your Clinical Research Manual to require new materials to be approved by the IRB before use. Please also provide documentation of any other 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.

Your response should reference "CTS # EC120380/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 New Jersey District Office, 10 Waterview Blvd, Third Floor, Parsippany, NJ 07054. 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/.

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,

Steven D. Silverman
Director
Office of Compliance
Center for Devices and
Radiological Health

cc:

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Biomed IRB
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